TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	ING117175: a Phase IIIb, randomized, open-label study of the safety and efficacy of dolutegravir or efavirenz each administered with two NRTIs in HIV-1-infected antiretroviral therapy-naïve adults starting treatment for rifampicin-sensitive tuberculosis

Compound Number: GSK1349572

Development Phase: IIIb

Effective Date: 10-JUL-2018

Protocol Amendment Number: 02

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N190475_00	2014-APR-24	Original
2014N190475_01	2016-MAR-21	Amendment No 1
Amended to include: change to the sample size from ~125 to ~115 (±5%) to alleviate the enrolment difficulties while maintaining a high power for the sample size assumption; clarification that the 2 month sputum TB culture to be performed on solid medium is preferred rather than mandated, correction of the list of participating countries, some minor clarifications to inclusion and exclusion criteria, clarification on the ability to perform GeneXpert testing (or equivalent validated test) at the Screening Visit, addition of investigator instructions on the new SAE review requirement in the eCRF, reformatting of Figure 6 to improve readability, and other minor clarifications and corrections of typographical errors.		
2014N190475_02	2018-JUL-10	Amendment No 2
Changes were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defects in infants born to women with exposure to dolutegravir at the time of conception. Changes were also made to update references to the DTG IB to reflect the most current versions. • The Risk Assessment table (Section 1.3.1, Table 1) was updated to include language regarding risk and mitigation of neural tube defects. • The inclusion criteria (Section 4.2) were updated to align the pregnancy information with more recent protocols. • The withdrawal criteria (Section 4.5) were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study. • The Time and Events table (Section 6.1, Table 2). was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy. • A new appendix was added detailing pregnancy information, including the modified list of highly effective methods for avoiding pregnancy in FRP and the collection of pregnancy data (Appendix 9, Section 11.9.1). The double barrier method of contraception, which does not meet updated GSK/ViiV criteria for a highly effective method, was excluded.		

SPONSOR SIGNATORY

PPD

7/10/18

Kimberly Y. SnPPD
Vice President (Strategy
ViiV Healthcare

Date

PPD

SPONSOR INFORMATION PAGE

Clinical Study Identifier: ING117175

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is implementing and managing all aspects of this study.

Sponsor Legal Registered Address:

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK
Telephone: PPD

Sponsor Contact Address

ViiV Healthcare Company
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Vice President, Global Research and Medical Strategy

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is supporting ViiV Healthcare in the conduct of this study

Medical Monitor and Serious Adverse Events (SAE) Contact Information:

PPD MD, PhD
PPD
3900 Paramount Parkway, South Building, 3rd Floor, Office 352
Morrisville, NC 27560-8408
Phone: PPD
Fax: PPD
PPD

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number ING117175:

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
BUN	Blood urea nitrogen
c/mL	Copies/milliliter
CDC	Centers for Disease Control and Prevention
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
C-SSRS	Columbia-Suicidality Severity Rating Scale
CI	Confidence interval
CPK	Creatine phosphokinase
CrCL	Creatinine clearance
CYP	Cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DHHS	United States Department of Health and Human Services
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DRV	Darunavir, Prezista
DRV/r	Darunavir + Ritonavir
DTG	Dolutegravir
ECG	Electrocardiograph
eCRF	Electronic case report form
EFV	Efavirenz, Sustiva
FDA	US Food and Drug Administration
FTC	Emtricitabine, Emtriva
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INI	Integrase inhibitor
INR	International normalized ratio
IP	Investigational product

IRB	Institutional Review Board
IRIS	Immune reconstitution inflammatory syndrome
ITT	Intent-to-treat
ITT-E	Intent-to-treat-exposed
IVRS	Interactive voice response system
LDL	Low-density lipoprotein
LN	Lymph node
mg	Milligram
MITT-E	Modified intent-to-treat
mL	Milliliter
MTB	*Mycobacterium tuberculosis*
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OLE	Open-label extension
PCR	Polymerase chain reaction
PGx	Pharmacogenetic
PI	Protease inhibitor
PK	Pharmacokinetic
PRO	Protease
PSRAE	Possible suicidality-related adverse event
PT	Prothrombin time
RAL	Raltegravir, Isentress
RAP	Reporting and analysis plan
RIF	Rifampicin
RNA	Ribonucleic acid
RT	Reverse transcriptase
SAE	Serious adverse event
SPM	Study Procedures Manual
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate, Viread
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine, Truvada
TMP-SMX	Trimethoprim-sulfamethoxazole
ULN	Upper limit of normal
VSLC	ViiV Safety and Labeling Committee
WHO	World Health Organization

Trademark Information

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM
KIVEXA
TIVICAY
TRIZIVIR
ZIAGEN

Trademarks not owned by ViiV Healthcare
Atripla
Complera
Efavirenz
Emtriva
GeneXpert
GenoSure
Isentress
MedDRA
Monogram Biosciences
PhenoSense
Quest Diagnostics
SAS
Standard Phenosense

PROTOCOL SUMMARY

Rationale

Study ING117175 is being conducted to assess the antiretroviral activity of a dolutegravir (DTG)-containing regimen (50 mg twice-daily during tuberculosis [TB] treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once-daily, with 2 nucleoside reverse transcriptase inhibitors [NRTIs]) in antiretroviral therapy (ART)-naïve patients with human immunodeficiency virus (HIV)-1 infection taking rifampicin (RIF)-containing first-line treatment for pulmonary, pleural, and lymph node (LN) RIF-sensitive TB. Safety, TB-associated immune reconstitution inflammatory syndrome (IRIS), and tolerability will also be explored. This study is designed to assess the antiviral activity of DTG and efavirenz (EFV) ART-containing regimens through 48 weeks.

Objectives

Primary Objective

To assess the antiviral activity at 48 weeks of a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily, with 2 NRTIs) in ART-naïve patients with HIV-1 infection taking RIF-containing TB treatment.

Secondary Objectives

- To assess the antiviral activity of DTG and EFV both administered with 2 NRTIs at Week 24;
- To assess the antiviral activity of EFV administered with 2 NRTIs at Week 48;
- To evaluate immunological activity (CD4+ lymphocyte [CD4 counts]) at Week 24 and Week 48;
- To evaluate the safety, TB-associated IRIS, and tolerability in subjects treated with a DTG- or EFV-based regimen concurrently with treatment for TB over time;
- To assess the development of HIV-1 resistance in subjects who meet confirmed virologic withdrawal criteria over 24 and 48 weeks.

Tertiary Objectives

- To evaluate the incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death) over time;
- To describe rates of TB treatment success (using the World Health Organization [WHO] definition) for all subjects;
- To describe the proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment;

- To evaluate concentrations of DTG and EFV using sparse sampling and to characterize DTG pharmacokinetics and variability during and post TB treatment and to explore the association between DTG and EFV concentrations and antiviral activity at Week 24 and Week 48.

Study Design

This is a Phase IIIb, randomized, open-label study describing the efficacy and safety of DTG and EFV-containing ART regimens in HIV/TB co-infected patients. The study will be conducted in approximately (± 5%) 115 HIV-1 infected individuals who are ART-naïve with a CD4+ cell count ≥50 cells/mm^3 and newly diagnosed with confirmed pulmonary, pleural, or LN *Mycobacterium* TB (MTB) taking RIF-containing first-line TB treatment. Subjects should have confirmed RIF-sensitive MTB infection as determined by GeneXpert (or equivalent approved molecular test) or mycobacterial culture. Eligible subjects will be randomly assigned in a 3:2 ratio to receive DTG plus 2 NRTIs (approximately 69 subjects) or EFV plus 2 NRTIs (approximately 46 subjects). The dual NRTI backbone will be selected by the investigator in accordance with local standard of care and per current WHO or national guidelines for the treatment of HIV/TB co-infected adults. Subjects randomization will be stratified by screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). An interim analysis will be conducted when all subjects complete their Week 24 visit, the primary Week 48 analysis will be conducted when the last subject completes the Randomized Phase, and a final end-of-study analysis will be conducted when the final subject randomly assigned to DTG has transitioned from the Open-Label Extension (OLE) to commercial supplies of DTG or is withdrawn for the study.

This study will include a Screening Period, a Randomized Phase (Day 1 to Week 48 plus a 4-week extension), and a DTG OLE.

Only protocol-defined dose reductions, modifications, or changes in the frequency of any components of each HIV regimen or TB treatment will be allowed at any time in this study, including during the Screening Period.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be promptly communicated to the study medical monitor.

Study Endpoints/Assessments

The primary endpoint for this study will be the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population in the DTG arm.

Secondary Efficacy Endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the EFV arm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related adverse event (AE), safety stopping criteria, or lack of efficacy);
- Changes from baseline in CD4+ counts at Week 24 and Week 48.

Tertiary Efficacy Endpoints

- Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses, and death);
- Proportion of subjects with TB treatment success (using the WHO definition);
- Proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment.

Safety endpoints will include: incidence and severity of AEs and laboratory abnormalities, proportion of subjects who discontinue treatment due to AEs, and proportion of subjects with TB-associated IRIS.

Pharmacokinetic endpoint will include an evaluation of concentrations of DTG and EFV measured at Weeks 8, 24, 36, and 48 using sparse sampling.

Virologic endpoint will be the incidence of treatment-emergent genotypic and phenotypic resistance to DTG, EFV, and other on-study ART in subjects meeting confirmed virologic withdrawal criteria over 24 and 48 weeks.

1. INTRODUCTION

1.1. Background

Approximately 14 million individuals worldwide are estimated to be dually infected with human immunodeficiency virus (HIV) and tuberculosis (TB). The yearly incidence of TB infection is about 10% among patients with HIV and TB is the most common cause of death in patients with HIV worldwide. HIV and TB co-infection have profound effects on the host's immune system. Recent studies evaluating the optimal timing for initiation of antiretroviral therapy (ART) in patients requiring treatment for active TB demonstrated a survival benefit for starting ART soon after TB treatment initiation rather than waiting until TB treatment completion. More specifically, current United States Department of Health and Human Services (DHHS) guidelines [DHHS, 2014] suggest that for patients with a CD4+ cell count <50 cells/mm^3, ART should be started within 2 weeks of starting TB treatment; for patients with a CD4+ cell count ≥50 cells/mm^3, ART should be started within 2 months of starting TB treatment [Török, 2011]. British guidelines suggest starting as soon as possible for patients with a CD4+ cell count ≤100 cells/mm^3 [British HIV Association (BHIVA) Guidelines, 2011]. As a result of the aforementioned studies and guidelines, there is an increase in the number of co-infected individuals being treated concurrently.

Currently, rifamycins (such as rifampicin [RIF]) serve as the cornerstone of TB therapy because of their unique sterilizing activity. No drug can adequately substitute for rifamycins in the TB regimen; if rifamycins cannot be used, treatment duration must be substantially prolonged (from 6 months to 9 to 24 months in most cases). TB treatment is given in 2 stages: during the first 2 months (intensive phase), patients with RIF-sensitive TB receive isoniazid (H), RIF (R), pyrazinamide (Z), and ethambutol (E) (HRZE), and during the subsequent 4 months (TB treatment continuation phase), patients receive isoniazid and RIF (HR). Some national guidelines recommend a TB treatment continuation phase of HR extended to 7 months in HIV and TB co-infected patients.

Rifampicin is the most commonly used rifamycin for TB treatment. It is a potent inducer of cytochrome P450 enzyme activity. By activating the pregnane X receptor (PXR), RIF can induce multiple metabolic enzymes, including cytochrome P450 (CYP) isoenzyme 3A (CYP3A), other CYP enzymes, Phase II drug-metabolizing enzymes, UDP-glucosyltransferases, sulfonyltransferases, and drug transporters. Since most protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) used to treat HIV are metabolized by CYP3A, induction of CYP3A by RIF can lead to reduced serum concentrations of antiretroviral drugs with risk of treatment failure or emergence of resistance to antiretroviral drugs. Nucleoside reverse transcriptase inhibitor (NRTI) concentrations, though, are not reduced by RIF in a clinically meaningful way. In patients who must be treated with RIF-containing TB therapy and require concurrent ART, efavirenz (EFV)-based ART can be used safely and effectively [Boulle, 2008; DHHS, 2013; WHO, 2010]. However, because the side effect profile of EFV (which includes treatment-related rash, CNS effects, and liver enzyme elevations) overlaps with the adverse effect profile of HRZE therapy, management of toxicity is complex. Integrase inhibitors (INI) may offer an important alternative to EFV-based therapy in TB co-

infected patients. Although the BHIVA guidelines recommend an increased dose of EFV of 800 mg for HIV/TB co-infected patients [BHIVA Guidelines, 2011], the DHHS, Centers for Disease Control and Prevention (CDC), and WHO TB guidelines do not recommend a dose increase of EFV [DHHS, 2014; WHO, 2010; CDC, 2013], because the evidence that RIF treatment impacts HIV antiviral responses with EFV-based combination ART is weak. In addition, among the minority of patients with lower levels of EFV during TB therapy, EFV concentrations remain above the required levels for adequate antiviral activity and an even lower dose of EFV has recently been shown to be effective. In the ENCORE study, the 400-mg once-daily dose of EFV in combination with tenofovir/emtricitabine (TDF/FTC) has been shown to be non-inferior to EFV 600 mg once daily with TDF/FTC at Week 48 in ART-naive patients [ENCORE1 Study Group, 2014].

Further, for those with contraindications or resistance to NNRTIs, there are few treatment options, as RIF cannot be used safely or effectively with PIs, even with dose adjustment. Substitution of rifabutin (RBT) for RIF is a reasonable TB treatment option for HIV/TB co-infected adults; however, because RBT is metabolized by CYP3A4, it requires bidirectional dose adjustment when given with PIs, and the optimal RBT dosing frequency is unknown. In addition, access to rifabutin is difficult in most resource-limited settings. The same potential drug interaction problem may occur when treating HIV/TB co-infection using recently developed antituberculosis drugs such as the diarylquinoline antimycobacterial drug bedaquiline, as exposure to this drug may be reduced during co-administration with inducers of CYP3A4 and increased during co-administration with inhibitors of CYP3A4 [Sirturo Product Information, 2013]. An antiretroviral drug that could be taken with an NRTI backbone and be used safely and effectively with RIF in the treatment of HIV/TB co-infection without the need for adjustments to the patient's TB regimen would give physicians and patients an important treatment option.

1.2. Rationale

In a Phase II open-label, randomized clinical study, the HIV INI raltegravir (RAL) was shown to be a suitable antiretroviral drug alternative to EFV for HIV/TB co-infected patients undergoing TB therapy study after 48 weeks of treatment (Grinsztejn, 2014). These results support the investigation of other INIs such as dolutegravir (DTG) in HIV/TB co-infection.

DTG is approved in the United States, Canada, the EU, Brazil, and in other countries, and is under review with other countries' regulatory agencies. Two Phase III studies, ING114467 (SINGLE) and ING113086 (SPRING-2) evaluated safety and efficacy of DTG in HIV-infected adults who were ART-naïve. ING114467 (SINGLE) evaluated the safety and efficacy of DTG 50 mg once daily plus FDC abacavir/lamivudine (ABC/3TC) 600 mg/300 mg compared with Atripla (EFV/FTC/TDF). Following 48 weeks of treatment, 88% of the subjects receiving DTG (50 mg once daily plus ABC/3TC) compared with 81% of the subjects receiving EFV/FTC/TDF had plasma HIV-1 RNA levels of <50 copies/mL; test for superiority had a p=0.003 [Walmsley, 2013]. ING113086 (SPRING-2) evaluated antiviral efficacy of DTG 50 mg once daily plus dual NRTI. After 48 weeks of treatment, 88% of the subjects receiving DTG (50 mg once daily plus TDF/FTC 300 mg/200 mg or ABC/3TC 600 mg/300 mg) compared with 85%

of those taking RAL (400 mg twice daily plus TDF/FTC 300 mg/200 mg or ABC/3TC 600 mg/300 mg) had plasma HIV-1 RNA levels of <50 copies/mL [Raffi, 2013a]. DTG was shown to be efficacious and non-inferior to RAL in combination with a dual NRTI. Non-inferiority between DTG and RAL was also demonstrated at Week 96 [Raffi, 2013b]. DTG 50 mg twice daily has also been studied in patients with INI-resistant virus in the VIKING and VIKING-3 studies and shown to be effective and well tolerated, with a safety profile comparable to that of DTG 50 mg once daily [Eron, 2013; Castagna, 2014]. Rates of discontinuation due to adverse events (AEs) were ≤2% in the DTG 50 mg once a day arms of the ART-naïve studies and ≤4% in the treatment-experienced population in the VIKING-3 study on DTG 50 mg twice a day with an optimized background regimen.

DTG is primarily metabolized by UGT1A1 with CYP3A4 as a minor route, and both enzymes are induced by RIF. Therefore a Phase I open-label, 3-period, fixed-sequence study was conducted in healthy, HIV-seronegative subjects, evaluating the pharmacokinetic (PK) and safety of DTG given alone at a dose of 50 mg once daily to that of DTG given at a dose of 50 mg twice daily together with steady-state RIF [Dooley, 2013]. Twice-daily DTG plus RIF achieved mean DTG concentrations that were 20%-33% higher than once-daily DTG dosing alone. Specifically, the geometric mean ratio for the 24-hour area under the time-concentration curve (AUC0-24), comparing DTG twice daily plus RIF with DTG once daily, was 1.33 (90% confidence interval [CI] 1.14 to 1.54). The GMR for the trough concentration at the end of the dosing interval (Cτ) was 1.22 (90% CI 1.01 to 1.48). There were no discontinuations for AEs and any Grade 3 or higher AEs. In summary, in this Phase I study, DTG at 50 mg twice daily given together with standard-dose RIF was well-tolerated and resulted in DTG concentrations similar to those of DTG 50 mg given once daily alone. Based on these results and as specified in the DTG prescribing information, the dose selection of twice-daily DTG 50 mg plus dual NRTI tablet during TB treatment was selected. The twice-daily regimen will be maintained for 2 weeks following discontinuation of TB treatment in order to eliminate (i.e., washout) the effects of RIF on the induction of UGT1A1 and CYP3A4; thereafter; once-daily DTG 50 mg with the same NRTI backbone will be administered through Week 48.

ART regimens using DTG 50 mg twice daily may represent a new treatment option for TB-infected patients who require concurrent treatment for HIV infection. This study will examine the use of DTG-based regimen among patients with HIV/TB co-infection.

1.3. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG can be found in the most current version of the Investigator's Brochure (IB) [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01]];. The following section outlines the risk assessment and mitigation strategy for the use of DTG as described in this protocol.

The approved country product labels should be referenced for RIF and all other components of the TB regimen, NRTIs, and EFV.

1.3.1. Risk Assessment

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Considerations when using DTG are presented in Table 1.

Table 1 Considerations When Using DTG

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG] Refer to IB for additional information on DTG		
Hypersensitivity and Rash	HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme were reported.	Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 4.3). Specific/detailed toxicity management guidance is provided for HSR (Section 6.4.3.5) and rash (Section 6.4.3.8). The subject informed consent form includes information on this risk and the actions subjects should take in the event of a rash or associated signs and symptoms.
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For subjects with hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG- containing ART contributed to significant elevations in liver chemistries. Drug-induced liver injury is a well-described adverse outcome of TB treatment. The risk of DILI from TB treatment is higher if the subject is also co-infected with HIV.	Subjects meeting either of the following criteria during the Screening Period are excluded from participating (Section 4.3). • Alanine aminotransferase (ALT) ≥2 times the upper limit of normal (ULN) • Subjects with an anticipated need for hepatitis C virus (HCV) therapy during the Randomized Phase (Day 1 to Week 48 plus a 4-week treatment extension) Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 6.4.3.1).
Theoretical serious drug interaction with dofetilide and pilsicainide	Co-administration of DTG may increase dofetilide/pilsicainide plasma concentration via inhibition of organic cation transporter 2 (OCT2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 5.6.2).
GI intolerance	Non-clinical studies showed upper and lower GI toxicity, including vomiting, diarrhoea and gastric erosions observed in monkey toxicology studies (thought to be related to local and not systemic toxicity). Mild to moderate GI intolerance (mainly diarrhoea and nausea) is associated	Routine monitoring of GI symptoms will be performed.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG] Refer to IB for additional information on DTG		
	with DTG treatment in a small proportion of subjects; however there were no indications of an increased risk for peptic ulcers or serious erosions.	
Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT2 receptor. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (Section 6.4.3.4).
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviours are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar or favourable compared with other ART. The reporting rate for insomnia was statistically higher for blinded DTG+ABC/3TC compared with EFV/TDF/FTC in ING114467; however, this was not duplicated in any other Phase IIb/III study conducted with DTG.	Subjects who in the investigator's judgment, poses a significant suicidality risk, are excluded from participating (Section 4.3). Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality will be monitored during this study. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour (Section 6.4.10).
Creatine phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	Specific detailed toxicity management guidance is provided for subjects who develop Grade 3 to 4 CPK elevations (Section 6.4.3.7).
DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 9, Section 11.9.1) during treatment and until 2 weeks after the last dose of study medication 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded. 3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG] Refer to IB for additional information on DTG		
		have study treatment discontinued and be withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit
Increased occurrence of immune reconstitution inflammatory syndrome (IRIS)	With rapid HIV-1 RNA decline and early recovery of CD4+ cell counts there could theoretically, be an increase in cases of IRIS. Based on medical adjudication of IRIS-like events in ING111762, ART-experienced (INI-naïve) subjects with hepatitis C virus co-infection receiving DTG may be at greater risk for IRIS than those receiving RAL, due to improved HIV virologic and immunologic responses with DTG compared with RAL.	Subjects will be monitored for signs and symptoms of TB-associated IRIS. Definitions on criteria for diagnosing these cases are provided in Section 6.4.6. Subjects will also have frequent liver chemistry monitoring. Robust liver chemistry stopping criteria and liver event follow-up assessments are included.

3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ALT = alanine aminotransferase, CPK = creatine phosphokinase, DILI = drug induced liver injury, DTG = dolutegravir, EFV = efavirenz, FTC = emtricitabine, GFR = glomerular filtration rate, GI = gastrointestinal, HCV = hepatitis C virus, IRIS = immune reconstitution inflammatory syndrome, TDF = tenofovir, OCT2 = organic cation transporter 2, ULN = upper limit of normal

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for HIV-infected patients). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of investigational product (IP), and will be followed to resolution as per sponsor's standard medical monitoring practices. Clinical safety data will be routinely reviewed in GSK Safety Review team meetings. This will include in-stream review of data from this clinical trial on a routine basis, review of aggregate data on a protocol and program basis when available, and review of competitor data from the literature.

Events will be monitored using SAE reports and alerts for Grade 3/4 laboratory toxicities (according to the Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity grading for HIV-infected patients as described in Section 11.3). Serious/severe events will be managed appropriately including, but not limited to, IP being withdrawn, and will be followed to resolution by the medical monitor. Further information on SAE reporting is described in Section 6.4.14.

Clinical safety data will be routinely reviewed in GSK Safety Review team meetings. This will include in-stream review of data from this clinical trial on a routine basis; review of aggregate data on a protocol and program basis when available; and review of competitor data from the literature.

1.3.2. Benefit Assessment

Early initiation of HAART together with HRZE therapy significantly reduces mortality in HIV-TB co-infected patients [DHHS, 2013]. Both EFV-based and RAL-based therapy have been shown to be effective for HIV/TB co-infected patients; in the REFLATE study, 48 week success rates with RAL 400 twice daily was 76% (95% CI 65-88), 63% (95% CI 49-76) with RAL 800 mg twice daily; and 67% (95% CI 54-80) with EFV, with no significant differences among the groups. Thirty-three percent to 37% of the subjects in each treatment group developed Grade 3 or higher AEs. These results suggest the possibility for improvements in treatment outcomes.

The safety profile for DTG 50 mg once daily was comparable to RAL and darunavir + ritonavir (DRV/r) and generally favorable to the EFV/TDF/FTC STR (Atripla) in both ART-naïve and ART-experienced (INI-naïve) patients (studies ING113086 [SPRING-2], ING111762 [SAILING], ING114915 [FLAMINGO] and ING114467 [SINGLE]). The most frequently observed AEs across patient populations were diarrhea, nausea, and headache, which were generally Grade 1 or 2 in severity, and typically did not lead to discontinuation from studies. With regards to antiviral efficacy, in treatment-naïve HIV-infected adult subjects, DTG 50 mg once daily was shown to be non-inferior to RAL in combination with a dual NRTI background regimen (SPRING-2). In study ING114915 (FLAMINGO), virologic suppression (HIV-1 RNA <50 c/mL) in the DTG arm (90%) was statistically superior to the DRV/r arm (83%) at Week 48. When used in combination with ABC/3TC, DTG was shown to be superior to EFV/TDF/FTC, a result driven by better tolerability of the DTG based regimen (SINGLE). In study ING111762 (SAILING), 71% of in INI-naïve ART-experienced patients receiving DTG achieved undetectable viral load (<50 c/ml) compared with 64% of those taking RAL at Week 48, reaching the threshold for statistical superiority [Cahn, 2013]. In the ING112574 (VIKING-3) study, DTG administered at 50 mg twice daily was demonstrated to be safe and effective in patients with INI resistance [Castagna, 2014, GlaxoSmithKline Document Number 2013N177327_00].

Study participants may also benefit from the medical tests and screening procedures performed as part of the study.

1.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with the DTG are justified by the anticipated benefits that may be afforded to HIV-1/TB co-infected ART-naïve adults.

2. OBJECTIVES

2.1. Primary Objective

To assess the antiviral activity at 48 weeks of a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily, with 2 NRTIs) in ART-naïve patients with HIV-1 infection taking RIF-containing TB treatment.

2.2. Secondary Objectives

- To assess the antiviral activity of DTG and EFV both administered with 2 NRTIs at Week 24;
- To assess the antiviral activity of EFV administered with 2 NRTIs at Week 48;
- To evaluate immunological activity (CD4+ lymphocyte [CD4 counts]) at Week 24 and Week 48;
- To evaluate the safety, TB-associated immune reconstitution inflammatory syndrome (IRIS), and tolerability in subjects treated with a DTG- or EFV-based regimen concurrently with treatment for TB over time;
- To assess the development of HIV-1 resistance in subjects who meet confirmed virologic withdrawal criteria over 24 and 48 weeks.

2.3. Tertiary Objectives

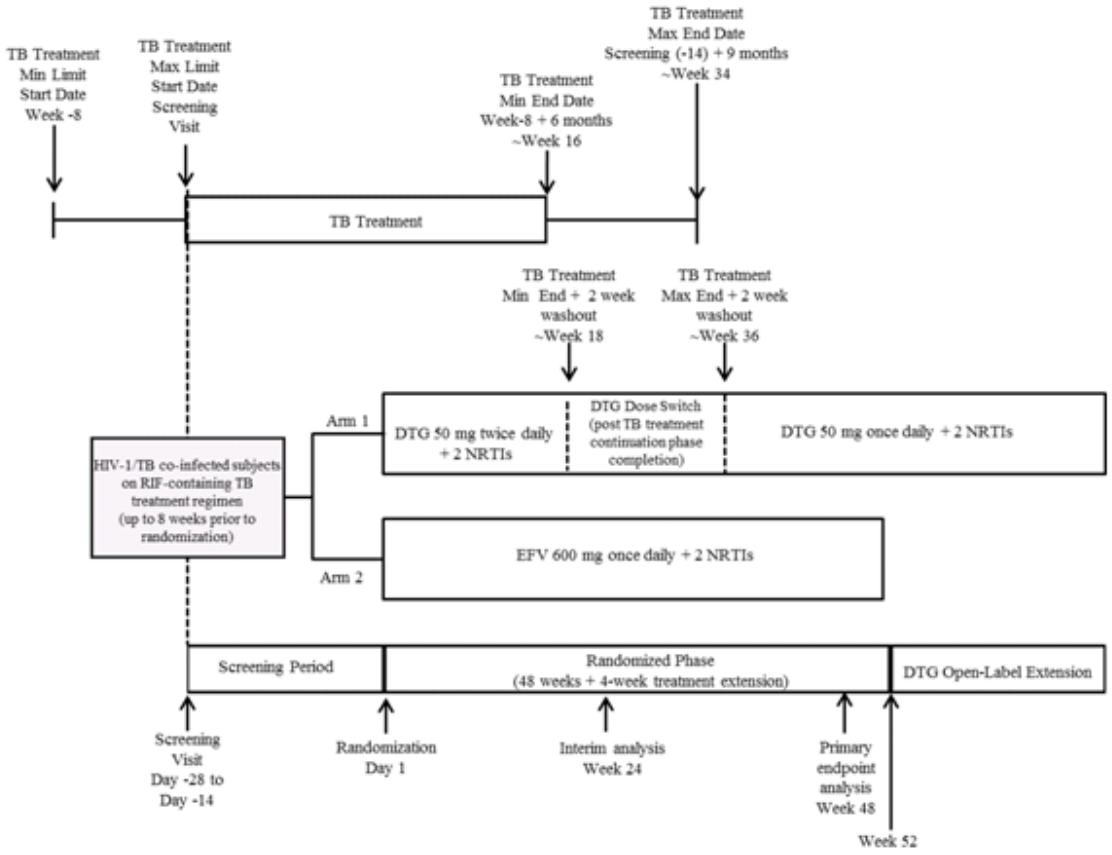
- To evaluate the incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death) over time;
- To describe rates of TB treatment success (using the WHO definition [WHO, 2010]) for all subjects;
- To describe the proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment;
- To evaluate concentrations of DTG and EFV using sparse sampling and to characterize DTG PK and variability during and post TB treatment and to explore the association between DTG and EFV concentrations and antiviral activity at Week 24 and Week 48.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a Phase IIIb, randomized, open-label study describing the efficacy and safety of DTG and EFV-containing ART regimens in HIV/TB co-infected patients. The study will be conducted in approximately (±5%) 115 HIV-1 infected individuals who are ART-naïve with a CD4+ cell count ≥50 cells/mm^3 and newly diagnosed with confirmed pulmonary, pleural, or LN *Mycobacterium* TB (MTB) taking RIF-containing first-line TB treatment. Subjects should have confirmed RIF-sensitive MTB infection as determined by GeneXpert (or equivalent approved molecular test) or mycobacterial culture.

Figure 1 Study Schematic



DTG = dolutegravir; EFV = efavirenz; max = maximum; mg = milligram; min = minimum; NRTI = nucleoside reverse transcriptase inhibitor; NTP = National TB Control Program; RIF = rifampicin; TB = tuberculosis

Note: TB treatment including isoniazid, RIF, pyrazinamide, and ethambutol will be provided at standard doses by the NTP under program conditions.

Eligible subjects will be randomly assigned in a 3:2 ratio to receive DTG plus 2 NRTIs (approximately 69 subjects) or EFV plus 2 NRTIs (approximately 46 subjects). The dual NRTI backbone will be selected by the investigator in accordance with local standard of care and per current WHO or national guidelines for the treatment of HIV/TB co-infected adults. Subjects randomization will be stratified by screening plasma HIV-1 RNA

(≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). An interim analysis will be conducted when all subjects complete their Week 24 visit, the primary Week 48 analysis will be conducted when the last subject completes the Randomized Phase, and a final end-of-study analysis will be conducted when the final subject randomly assigned to DTG has transitioned from the Open-Label Extension (OLE) to commercial supplies of DTG or is withdrawn for the study.

This study will include a Screening Period, a Randomized Phase (Day 1 to 48 weeks plus a 4-week extension), and a DTG OLE.

Only protocol-defined dose reductions, modifications, or changes in the frequency of any components of HIV regimen or TB treatment will be allowed at any time in this study, including during the Screening Period (Section 5.1.5).

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 2), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be promptly communicated to the study medical monitor.

3.1.1. Screening Period

TB diagnosis and confirmation of RIF-sensitive MTB infection must be performed locally. If the result confirming MTB infection is not available before the subject is screened, the assessment can be performed simultaneously in order to screen the subject for the study. Subjects with RIF-resistant TB are not eligible to enter the study. GeneXpert or other molecular test result is required to rule out RIF resistance prior to entry. Mycobacterial culture may be used to confirm RIF-sensitivity (as an alternative to GeneXpert or molecular testing) provided the culture results are available prior to randomization. The 14-day Screening Period may be extended to 28 days to allow receipt of all screening assessment results and to accommodate scheduling. Subjects are allowed to re-screen for this study one time; this will require a new subject ID number. A single repeat test (retest) per analyte or assessment is allowed during the Screening Period to determine eligibility, except for HIV drug resistance testing.

3.1.2. Randomized Phase (Day 1 to Week 48 plus 4-Week Extension)

As soon as all screening results are available, subjects who fulfill all eligibility requirements will be randomly assigned in a 3:2 ratio to receive either DTG or EFV-containing regimens, respectively. DTG or EFV regimens will be started up to 8 weeks after TB treatment initiation and will continue for 48 weeks, plus a 4-week extension.

TB treatment consisting of HRZE for 2 months (i.e., TB treatment intensive phase) followed by HR for 4 or 7 months (i.e., TB treatment continuation phase) will be administered according to local guidelines with TB treatment provided by the National TB Control Programs (NTP) in accordance with national guidelines. Sputum will be collected from subjects with pulmonary tuberculosis 2 months after initiating TB treatment (solid media culture testing is preferred). Sputum will also be collected at

4 months, 6 months, and 9 months (for subjects who receive TB treatment for 9 months) for smear and culture, for as long as the subject is able to produce sputum. Sputum samples are not required from subjects diagnosed only from pleural or LN aspirates that do not also have pulmonary disease. The same laboratory and method of MTB culture must be used during the study.

Subjects assigned to Arm 1 will receive DTG 50 mg twice-daily with 2 NRTIs until 2 weeks after TB therapy is completed then they will receive DTG 50 mg once daily (with the same NRTI backbone) through the end of the Randomized Phase. Subjects randomized to Arm 2 will receive EFV 600 mg once daily plus 2 NRTIs through the end of the Randomized Phase. The NRTI background regimen selected by the investigator must be determined and documented prior to randomization and should be composed of 2 NRTIs in accordance with the local standard of care and per the WHO or national treatment guidelines for HIV/TB co-infection. Following Day 1, no changes or intensification of background regimen will be permitted prior to meeting confirmed virologic withdrawal criteria or Week 52, with the exception of one allowed background NRTI change for management of drug toxicity as described in Section 6.4.3.

Subjects randomization will be stratified by screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). DTG and EFV will be administered in an open-label fashion throughout the Randomized Phase.

During the Randomized Phase, subjects will attend the clinic at Baseline/Day 1 and at Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

Following the Week 48 visit, subjects will remain on their DTG or EFV-containing regimen for an additional 4 weeks. All subjects will attend the Week 52 visit, although only those with a viral load of ≥50 c/mL at Week 48 will have their viral load confirmed by an assessment at the Week 52 visit. This treatment extension will allow for a more accurate assessment of treatment response for the Week 48 analysis window, as transient increases of HIV-1 RNA levels ≥50 c/mL will not be classified as virologic failure.

To determine DTG and EFV concentrations, sparse plasma samples will be collected at Weeks 8, 24, 36, and 48 in as many subjects as possible. If a subject meets virologic withdrawal criteria, HIV-1 resistance testing will be performed to assess treatment emergent mutations for INIs, NNRTIs, and NRTIs.

3.1.3. DTG Open-Label Extension

Only those subjects randomized to receive DTG plus 2 NRTIs will enter into the DTG OLE.

If DTG is locally approved and commercially available when a subject successfully completes the Randomized Phase, the subject will be considered to have completed the study (see Section 3.1.5) and will need to have alternate arrangements in place to access DTG and NRTIs. If DTG is not locally approved and commercially available when a subject successfully completes the Randomized Phase, he/she will have the opportunity

to enter into the DTG OLE. During the DTG OLE, subjects will be supplied with DTG until it is locally approved and commercially available, the subject no longer derives clinical benefit, or the subject meets a protocol-defined reason for discontinuation. Subjects who enter the DTG OLE will be monitored accordingly every 12 weeks.

3.1.4. Study Completion

Subjects are considered to have completed the study if they satisfy one of the following:

- Randomized to EFV plus 2 NRTIs and completed the Randomized Phase including the Week 52 visit;
- Randomized to DTG plus 2 NRTIs and completed the Randomized Phase including the Week 52 visit; and did not enter the DTG OLE;
- Randomized to DTG plus 2 NRTIs, completed the Randomized Phase, including the Week 52 study visit, and entered and completed the DTG OLE (defined as remaining on study until commercial supplies of DTG become locally available).

3.1.5. Follow-up

Subjects with ongoing AEs or laboratory abnormalities will attend a Follow-up visit approximately 4 weeks after their last dose of investigational product (IP) (DTG or EFV). Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality). The Follow-up visit is not required for successful completion of the study.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2. Discussion of Design

This randomized, open-label, multicenter, parallel group study design aims at assessing DTG antiviral activity in a sufficient number of subjects to demonstrate a clinically acceptable level of activity in HIV/TB co-infected patients receiving concomitant TB therapy.

Adult subjects diagnosed (smear positive) and proven RIF-sensitive TB who are initiating TB treatment with HRZE will be recruited at sites in Brazil, Mexico, Russia, Argentina, Peru, South Africa and Thailand. These areas were selected based on epidemiology which suggests high rates of HIV and TB co-infection (WHO). Global Tuberculosis Report, 2013).

The primary endpoint, proportion of subjects at Week 48 with plasma HIV-1 RNA <50 c/mL, is a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression.

Efavirenz-based regimens are the preferred regimens for patients with HIV and TB coinfection because of complications arising from drug interactions with other agents. In this study, the use of EFV as the active control in (HIV) therapy-naïve patients with TB is justified based on its indication as an appropriate agent as first-line therapy in treatment-naïve HIV-1-infected adults in WHO, CDC, and EACS guidelines.

DTG has been extensively studied in Phase II and Phase III studies in a variety of HIV-1 patient populations (e.g., treatment-naïve, treatment-experienced [integrase naïve], and treatment-experienced [integrase resistant]). DTG with dual NRTI therapy has not been evaluated in HIV/TB co-infected subjects taking RIF. This study will provide important information regarding the efficacy, safety and tolerability, incidence of TB-associated IRIS, and PK of DTG plus 2 NRTIs as a first-line ART regimen in HIV/TB co-infected subjects receiving concomitant TB therapy.

The use of DTG at the 50 mg twice-daily dose is in accordance with DTG global labeling information (i.e., United States and the EU) [DTG US Prescribing Information, 2013; EU SmPC, 2014] when dosed with RIF and is based on the results of the PK drug-drug interaction study with both drugs [Dooley, 2013]. The DTG 50 mg twice-daily dose is continued 2 weeks after completion of the TB treatment course, after which RIF enzyme induction would be minimal.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

A sufficient number of subjects will be screened in order to ensure that a total of approximately (±5%) 115 subjects will be randomly assigned in a 3:2 ratio to DTG (approximately 69 subjects) and EFV (approximately 46 subjects), respectively.

Assuming 55% of subjects do not meet eligibility criteria, this will require the screening of approximately 255 subjects. Subjects will be enrolled from Brazil, Mexico, Russia, Argentina, Peru, South Africa and Thailand.

	Subjects
Screened	~255
Randomized	~115
Evaluable	~115

The primary analysis will use all subjects in the intent-to-treat exposed (ITT-E) population, consisting of randomly assigned subjects who receive at least one dose of study drug. Since the intent is for all randomly assigned subjects to receive study drug, the number of evaluable subjects should equal the number randomized subjects.

Further details of sample size assumptions are found in Section 8.1.1.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GlaxoSmithKline (GSK) investigational product or other study treatment that may impact subject eligibility is provided in the IB.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following are study-specific eligibility criteria unless stated otherwise. In addition to these criteria, investigators must exercise clinical discretion regarding selection of appropriate study subjects, taking into consideration any local treatment practices or guidelines and Good Clinical Practice (GCP). Specifically, investigators must follow national treatment guidelines for ART initiation for HIV/TB co-infected adults. Investigators must also ensure that HIV care for study subjects is available and will be provided locally after study completion. Study completion is described in Section 3.1.4.

Eligible subjects must:

- Be able to understand and comply with protocol requirements, instructions, and restrictions,
- Be likely to complete the study as planned,
- Be considered appropriate candidates for participation in an investigative clinical trial with oral medication (e.g., no active substance abuse, acute major organ disease). It is of note that alcohol abuse would make these subjects more prone to develop TB-treatment–related liver-related toxicities.

Except for TB diagnosis laboratory test to determine eligibility that is to be performed locally, laboratory results from the central laboratory services provided by this study will be used to assess eligibility. Subjects not meeting all inclusion and exclusion criteria at the initial Screening visit may be rescreened **only once;** the subject will receive a new subject number. With the exception of a disqualifying viral genotype, a single repeat test (re-test) per analyte or assessment is allowed during the Screening Period to determine eligibility.

Subjects eligible for enrollment in this study must meet all of the following:

1. Subject or the subject's legal representative is willing and able to understand and provide signed and dated written informed consent prior to Screening;
2. Subject has plasma HIV-1 RNA ≥1000 copies/mL at Screening;
3. CD4+ cell count is ≥50 cells/mm^3 at Screening;
4. Subject is ≥18 years of age;
5. HIV-1-infected, ART-naïve; (≤10 days of prior therapy with any antiretroviral drug following a diagnosis of HIV-1 infection);
6. A female subject may be eligible to enter and participate in the study if she:

a. is of non-childbearing potential defined as either postmenopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy, or bilateral oophorectomy or,

b. is of childbearing potential, with a negative pregnancy test at both Screening and Day 1, and agrees to use one of the following methods of contraception to avoid pregnancy throughout the study and for at least two weeks after discontinuation of all study medication (see Appendix 9, Section 11.9):

- Complete abstinence from penile-vaginal intercourse from 2 weeks prior to administration of IP, throughout the study, and for at least 2 weeks after discontinuation of all study medications. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Approved hormonal contraception (see Appendix 9, Section 11.9)plus a barrier method while receiving RIF-containing TB treatment for subjects randomly assigned to the DTG arm and then regardless of use of a barrier method after discontinuation of RIF-containing TB treatment, or approved hormonal contraception plus a barrier method for subjects randomly assigned to the EFV arm (regardless of RIF-containing TB treatment). Approved hormonal contraception including:
    - Combined oestrogen and progestogen oral contraceptive [Hatcher, 2011])
    - Contraceptive subdermal implant
    - Injectable progestogen [Hatcher, 2011]
    - Contraceptive vaginal ring [Hatcher, 2011]
    - Percutaneous contraceptive patches [Hatcher, 2011] ;
- Any intrauterine device (IUD) or intrauterine system;
- Male partner sterilization with documentation of azoospermia *prior to the female subject's entry* into the study and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.;
- Any other method with published data showing that the expected failure rate is <1% per year.

Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of study drug. A childbearing potential female subject who starts the study using complete abstinence as her contraceptive method and decides to become sexually active must use the double barrier method either as a bridge to an approved hormonal contraception (if possible) or as a method of choice to be maintained from that moment onwards.

All subjects participating in the study should be counseled on safer sexual practices including the use of effective barrier methods (e.g. male condom/ spermicide).

Note: these contraceptive requirements do not apply to females of childbearing potential with same sex partners only, when this is their preferred and usual lifestyle.

7. New diagnosis of pulmonary, pleural, or LN tuberculosis based on identification of Mycobacterium tuberculosis using culture methods or GeneXpert (or other approved molecular test) on sputum or on samples collected by needle aspirate of pleural fluid or an affected LN;
8. RIF sensitivity of *Mycobacterium tuberculosis* either by culture or Gene Xpert (or other approved nucleic acid amplification test);
9. RIF-containing first-line TB treatment or an alternate RIF-containing TB treatment as described in Section 11.6 started up to a maximum of 8 weeks before randomization and no later than the screening date;
10. Karnofsky score ≥70% before randomization (see Section 11.7).

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

Exclusionary Medical Conditions

1. Any previous TB treatment (not including treatment for latent disease);
2. Evidence of RIF resistance of *Mycobacterium tuberculosis* either by culture or Gene Xpert (or other validated nucleic acid amplification test);
3. Expected requirement for TB treatment >9 months;
4. Concomitant disorders or conditions for which isoniazid, RIF, pyrazinamide, or ethambutol are contraindicated;
5. Central nervous system, miliary, or pericardial TB;
6. Women who are pregnant or breastfeeding;
7. Any evidence of an active AIDS-defining disease (CDC Category C; see Section 11.2). Exceptions include TB, cutaneous Kaposi's sarcoma not requiring systemic therapy, and historic CD4+ cell counts of <200 cells/mm^3;
8. Subjects with moderate to severe hepatic impairment (Class B or C) as determined by Child-Pugh classification (see Section 11.8); unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, or known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones);
9. Subjects positive for hepatitis B surface antigen (HBsAg) at screening;
10. Anticipated need for hepatitis C virus (HCV) therapy during the Randomized Phase of the study;

11. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class;
12. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the study medical monitor for inclusion of the subject;
13. Subjects who, in the investigator's judgment, pose a significant suicidality risk. Recent history of suicidal behavior and/or suicidal ideation may be considered as evidence of serious suicide risk.

Exclusionary Treatments Prior to Screening or Day 1

14. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening;
15. Treatment with any of the following agents within 28 days of Screening: radiation therapy, cytotoxic chemotherapeutic agents, any immunomodulators that alter immune response;
16. Treatment with any agent, other than licensed ART as allowed above (Section 4.2, inclusion criterion 5), with documented activity against HIV-1 in vitro/vivo within 28 days of first dose of the investigational product (IP);
17. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP;

Exclusionary Laboratory Values or Clinical Assessments at Screening

18. Any evidence of primary viral resistance to NRTIs, NNRTIs, or PIs based on the presence of any major resistance-associated mutation [IAS USA, 2013] in the Screening result or, if known, any historical resistance test result. Note: Retests of Screening genotypes are not allowed;
19. Any verified Grade 4 laboratory abnormality with the exception of Grade 4 triglycerides. A single repeat test is allowed during the Screening period to verify a result;
20. Any acute laboratory abnormality at Screening, which, in the opinion of the investigator, would preclude the subject's participation in the study of an investigational compound;
21. Alanine aminotransferase (ALT) ≥2 × upper limit of normal (ULN);
22. Hemoglobin ≤7.4 g/dL;
23. Platelet count <50,000/mm^3.

Notwithstanding these minimum inclusion and exclusion criteria, investigators must also follow country-specific guidelines where they exist when making decisions about subjects who are eligible for study participation.

4.4. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the IP, background NRTIs, and TB treatment.

4.5. Withdrawal Criteria

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. Withdrawn subjects will not be replaced.

Subjects permanently discontinuing study treatments prior to Week 52 are considered to be withdrawn from the study treatments and also from the study. Similarly, subjects in the DTG arm who enter the DTG OLE but permanently discontinue participation prior to commercial supplies of DTG becoming locally available (e.g., through public health services) are considered to be withdrawn from study treatment as well as from the study.

Subjects <u>may</u> be prematurely discontinued from the study for any of the following reasons:

- Subject or investigator non-compliance;
- At the request of the subject, investigator, or sponsor;
- The subject requires concurrent prohibited medications during the course of the study. However, the subject may remain in the study if in the opinion of the investigator and the medical monitor such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the subject.

Subjects <u>must</u> be prematurely discontinued from the study for any of the following reasons:

- Confirmed virologic withdrawal criteria as specified in Section 4.6.1.
- Subject requires changes (i.e., substitution or dose modification) of DTG or EFV. Permitted NRTI substitutions due to toxicity management are discussed in Section 5.1.5.
- Subject requires a TB treatment regimen that does not contain RIF.
- Subject requires interruption to RIF-containing regimens for longer than 14 days and is not on a bridging regimen. Permitted RIF-containing regimens are described in Section 11.6. Suitable bridging regimens are described in Section 6.4.3.1.1.
- Liver toxicity where stopping criteria specified in Section 6.4.3.1 are met and no compelling alternate cause is identified;
- Grade 4 clinical AE considered causally related to study drug or any component of TB treatment;

- Renal stopping criteria as described in Section 6.4.3.4 are met and no compelling alternate cause is identified;
- Hypersensitivity and rash criteria as described in Section 6.4.3.5 and Section 6.4.3.8, respectively are met and no compelling alternate cause is identified;
- Petechial rash due to RIF-induced thrombocytopenia as described in Section 6.4.3.9
- Pregnancy (intrauterine), regardless of termination status of pregnancy. As a reminder, females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.

If a subject is withdrawn from the study, the protocol-defined assessments (if withdrawn at a routine study visit), the Withdrawal visit assessments, and if necessary the Follow-up visit assessments described in the Time and Events Table (Table 2) should be performed. All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any subject from the study. A Follow-up visit may occur approximately 4 weeks after the last dose of study treatment and is only required in subjects with ongoing serious AEs (SAEs) or non-serious laboratory or clinical AEs at the time of withdrawal.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (e.g., telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the electronic case report form (eCRF).

Subjects are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the Completion/Withdrawal section of the eCRF. Every effort should be made by the investigator to follow-up with subjects who withdraw from the study. In the event that a subject is prematurely discontinued from the study at any time due to an AE (see Section 6.4.4.1), the procedures stated in the Time and Events Table (Table 2) must be followed. Subjects who are withdrawn from the study will not be replaced.

Subjects may have a temporary interruption to their study treatment for management of toxicities.

4.6. Virologic Criteria for Subject Management and Viral Resistance Testing

Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 24 or beyond must have HIV-1 levels re-assessed using the algorithms in Figure 2 and Figure 3, which detail virologic criteria for **clinical management** of subjects who either require more careful monitoring (e.g., meet "**4-6 week plasma HIV-1 RNA testing criterion**") or have met a "**suspected or confirmed virologic withdrawal criterion.**" Investigators should not schedule re-assessment blood draws to take place in the presence of factors that could be associated with HIV-1 RNA levels ≥50 c/mL, such as intercurrent acute infection, treatment interruption due to toxicity management or non-compliance, or vaccination. Subjects should have received full doses of IP for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL.

If a subject meets the confirmed virologic withdrawal criteria, the plasma 'for storage sample' from the "suspected virologic withdrawal criterion" visit and the Day 1 sample will be used for HIV-1 genotype/phenotype testing. Subjects may continue to receive IP at the discretion of the investigator until results of resistance testing are available, at which time the subject must be discontinued from the study. If a subject is prematurely discontinued from the study, the investigator must make every effort to perform the evaluations outlined in the Time and Events Table (Section 6.1). These data will be recorded as they comprise essential evaluations needed to be done before discharging any subject from the study.

Note: Plasma samples with <400 c/mL of HIV-1 RNA will not be analyzed for viral resistance, as the protease/reverse transcriptase/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <400 c/mL.

Figure 2 Virologic Criteria for Subject Management at Week 24

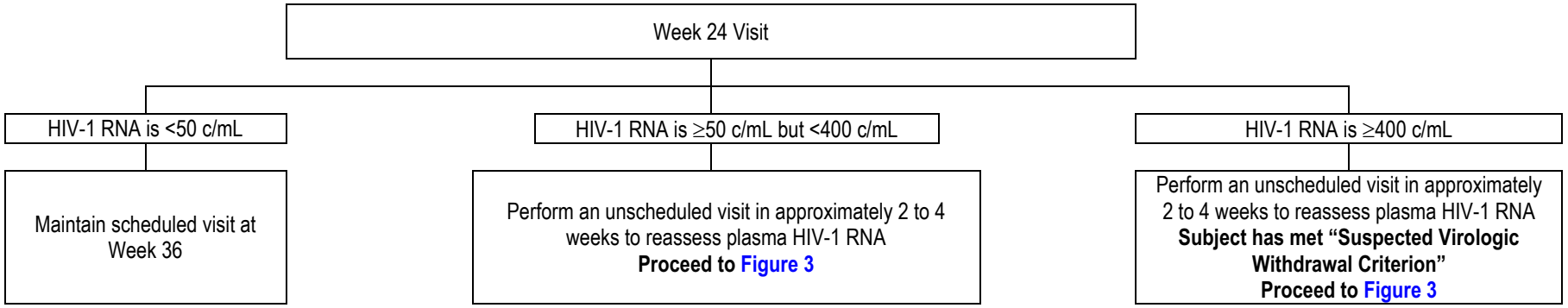
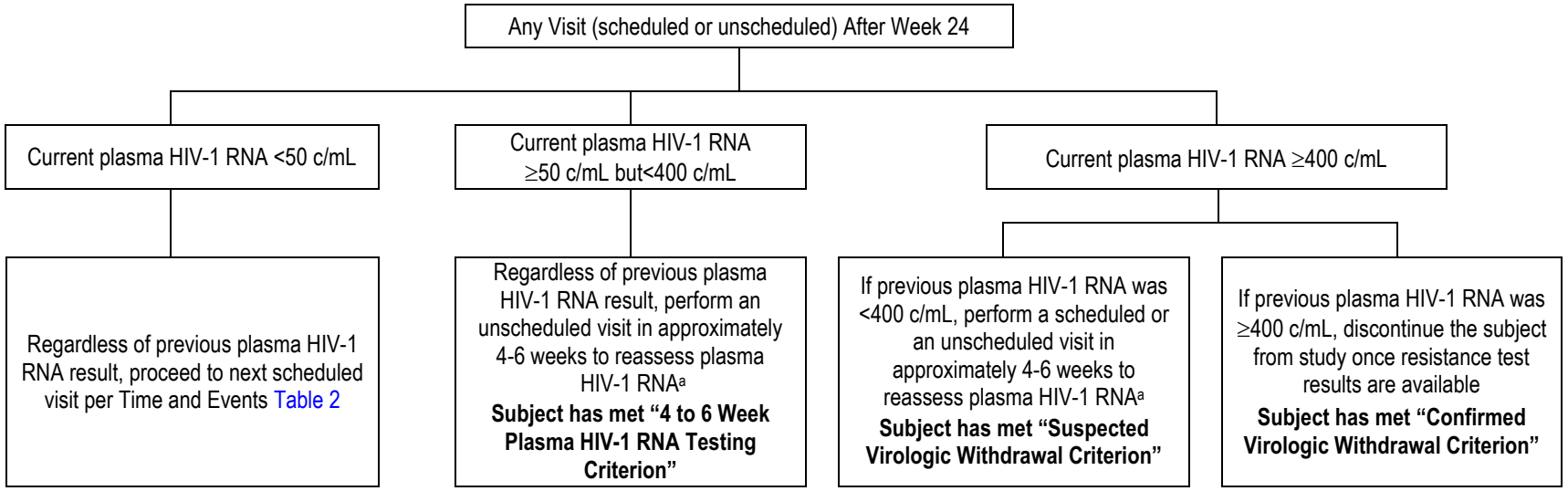


Figure 3 Virologic Criteria for Subject Management After Week 24



a. If current visit is the Week 48 scheduled visit then retest will occur at the Week 52 visit.

4.6.1. Management of Subjects Meeting Suspected Virologic Withdrawal Criteria

Only plasma HIV-1 RNA levels determined by the central laboratory (or a laboratory contracted by the central laboratory) will be used to assess virologic withdrawal criteria. Upon notification that a subject's plasma HIV-1 RNA level qualifies as meeting a suspected virologic withdrawal criterion, the investigator should query the subject regarding intercurrent illness, recent immunization, or interruption of therapy as inadequate adherence is a common cause of elevated HIV-1 RNA measurements.

All cases that meet a suspected virologic withdrawal criterion must be confirmed by a second measurement performed 4 to 6 weeks apart from the date of the original sample, unless one of the extenuating circumstances outlined below applies.

The following guidelines will be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the subject should receive full dose of all IP.
- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the subject should receive full dose of IP.
- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dose of IP.
- The subject should have received full doses of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

Sites should contact GSK to discuss individual subjects, whenever necessary.

At Week 48, repeat HIV-1 RNA testing is required for any HIV-1 RNA ≥50 c/mL and must be performed at the Week 52 study visit (Section 4.7).

4.7. Retest Criteria for Subjects With Plasma HIV-1 RNA Levels ≥ 50 c/mL at Week 48

Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 48 must have HIV-1 levels re-assessed by a second measurement performed at the Week 52 visit. Subjects should have received full doses of IP for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL.

Subjects with plasma HIV-1 RNA levels ≥400 c/mL should have a second measurement performed as outlined in Section 4.6.1.

4.8. Protocol-Defined Failure of TB Treatment

Tuberculosis treatment failure is defined by WHO [WHO, 2010] as patients whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant strain at any point of time during the treatment, whether they are smear-negative or smear-positive.

Subjects with suspected TB treatment failure should be evaluated with a history, physical examination, sputum smear and culture with drug-susceptibility testing, and chest radiograph (TB treating physicians caring for the subject and local investigators should also use clinical judgment to determine if other evaluations are required) to determine whether they have clinically responded to therapy, even though their cultures have not converted or were not tested. The initial culture results and drug-resistance tests, treatment regimen, and adherence also should be reviewed. Samples from all available sites should be taken for repeat culture and drug-susceptibility testing, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or superinfection with a drug-resistant strain. If the results of repeat cultures and rapid resistance testing confirm, in consultation with an expert in the field, that the subject will require broadening of TB treatment by switching to a second-line TB treatment regimen without RIF then the subject must be withdrawn from the study.

4.9. Screening Failures

A subject is considered a screen failure if after providing informed consent, the subject's circumstances or conditions change or the outcome of a test or assessment becomes available which results in the subject's failure to meet one or more of the entry criteria, or results in the investigator deciding that the subject is no longer an appropriate study candidate.

Subjects who meet all entry criteria are randomized and assigned a randomization number. Subjects not meeting all inclusion and exclusion criteria at the initial screen may be rescreened **only once** and the subject will receive a new subject number at that time. With the exception of disqualifying viral genotype or TB culture or nucleic-acid–based RIF-susceptibility results indicating RIF resistance, a single repeat test (retest) per analyte or assessment is allowed during the Screening Period to determine eligibility. Subjects who are randomized into the study and subsequently withdrawn from the study for any reason may not be rescreened.

Except for results to confirm MTB which are analyzed locally, laboratory results from the central laboratory services provided by this study will be used to assess eligibility.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

Investigational product in this protocol refers to the investigational drugs DTG and the active control EFV. These will be supplied by GSK. For the purpose of this protocol, other ARTs administered in the study are not considered IP and will not be supplied by GSK. These will be sourced as local commercial material. Investigators will select a dual NRTI background for each subject. Tuberculosis drugs are also not considered IP and will be provided by the local TB program in accordance with national and local guidelines.

The contents of the label will be in accordance with all applicable regulatory requirements.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IP will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Adequate precautions must be taken to avoid direct contact with the investigational product which should be used in accordance with the manufacturer's instructions detailed in the prescribing information.

5.1.1. Tablet Formulation of DTG

DTG tablets are packaged as a full count of 30 film-coated tablets in a 45 cc high density polyethylene (HDPE) bottles with induction seal and child-resistant 33 mm closure. Tablets must be stored in the original package with the bottle tightly closed. The bottles contain a desiccant that must be kept in the bottle to protect tablets from moisture. The recommended storage conditions and expiry date where required, are stated on the product label.

Subjects must keep all IP in its original pack container. GSK will notify sites if and when data are available to support the use of pill boxes.

5.1.2. Tablet Formulation of EFV

EFV [Sustiva (efavirenz) US Product Information, 2013; Sustiva Summary of Product Information, 2014] is supplied as the EFV oral tablet, which contains 600 mg of EFV. EFV tablets, as manufactured by Bristol Myers Squibb, are yellow film-coated capsule-shaped tablets printed with "SUSTIVA" on both sides. Each pack/bottle will contain 30 film-coated tablets.

5.1.3. Background NRTIs

The investigator-selected dual NRTI background regimen must be determined and documented prior to randomization.

All background NRTIs are locally registered products. GSK will not reimburse or supply the investigator-selected background regimen unless required by the local regulatory authority or Institutional Review Board/Independent Ethics Committee (IRB/IEC) or unless previously agreed with study sites.

Those subjects for whom abacavir (ABC) is being considered as a component of the NRTI backbone should have been screened and be negative for the human leukocyte antigen (*HLA*)-*B*5701* allele before randomization takes place. This testing may be conducted as part of the study or may be performed by local laboratories. Results must be available for source document verification.

5.1.4. Dosage and Administration

	IP and background NRTI Dose and Dose Interval
Treatment Arm 1	
GSK1349572 (dolutegravir, DTG)	Twice-daily DTG 50 mg plus dual NRTI during TB treatment and for 2 weeks[a] following discontinuation of TB treatment, then once-daily DTG 50 mg with the same NRTI backbone through Week 52 and continued during the DTG OLE until DTG is locally approved and commercially available
Treatment Arm 2	
Efavirenz (EFV)	Once-daily EFV 600 mg plus dual NRTI through Week 52

Note: TB treatment including isoniazid, RIF, pyrazinamide, and ethambutol will be provided at standard doses by the NTP under program conditions.

a. Delays in switching from DTG twice daily to DTG once daily will not be considered an overdose.

DTG may be administered with or without food. EFV must be administered without food. For the dual NRTIs refer to the appropriate NRTI product information for treatment administration.

5.1.5. Protocol-Permitted Substitutions

A substitution of or switch between DTG or EFV is not allowed.

After consultation with the study medical monitor, switch of background NRTI therapy to an alternate approved NRTI therapy for toxicity or tolerability management is allowed one time. Switches of a background NRTI for any reason other than toxicity or tolerability management are not permitted in the study. The date of the decision to switch background NRTI for toxicity or tolerability management must be documented in the eCRF.

Note: Protocol-permitted substitutions (as described above), will not be coded as failures in this study regardless of the subject's HIV-1 RNA results at the time of the protocol-permitted substitution (Section 8.2.4).

Further information regarding alternate RIF-containing TB treatment regimens are described in Section 11.6.

5.2. Treatment Assignment

Informed consent must be obtained prior to any study procedures, including any screening assessment.

Subjects will be assigned to study treatment in accordance with the randomization schedule. Randomization will be conducted using a central randomization procedure following confirmation of fulfillment of study entry criteria. Subjects will be assigned (3:2 ratio to DTG or EFV-containing regimens, respectively) to study treatment in accordance with the computer-generated randomization schedule. The central randomization schedule will be generated by biostatistics using a validated SAS developed program. The stratification will be generated using an interactive voice response system (IVRS). Study site personnel will be required to contact the central randomization service for assignment of a unique identifier (designating the subject's randomization code) for each subject participating in the study. A unique treatment number will be assigned for each subject participating in the study.

Subjects who are randomly assigned into the study and subsequently withdrawn may not be rescreened.

5.3. Blinding

This will be an open-label study.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of study drug dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to PPD, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Treatment adherence will be evaluated using pill counts of unused study drug (DTG and EFV). This assessment will be conducted each time the subject receives a new (refill) supply of study drug through the Withdrawal visit or study completion. These data will be recorded in the subject's eCRF but will not be summarized for analysis purposes.

Data on start and end dates for TB treatment or ART including periods of interruptions (if applicable) will be documented.

5.6. Concomitant Medications and Non-Drug Therapies

Subjects should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential drug-drug interactions between such treatments and the study drugs. All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name and the dates of administration are to be recorded.

5.6.1. Permitted Medications and Non-Drug Therapies

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 5.6.2). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the subject and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn and only once scheduled visits are ≥4 weeks apart. This approach will minimize the risk of nonspecific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

Daily doses of RIF should be given at least 1 hour before the ingestion of antacids.

DTG should be administered 2 hours before or 6 hours after taking antacid products or sucralfate containing divalent cations (e.g., aluminum and magnesium) or calcium or iron supplements; alternatively, DTG can be taken together with calcium or iron supplement with a meal. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration of DTG with multivitamins is acceptable.

Metformin concentrations may be increased by DTG. Subjects taking DTG should be monitored for glucose control during therapy and a metformin dose adjustment may be required.

5.6.2. Prohibited Medications and Non-Drug Therapies

The following concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines (see Section 5.6.1 for guidance regarding non-HIV vaccines)
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy (see Exclusion Criteria, Section 4.3)
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited through the Randomized Phase (Day 1 to Week 48 plus a 4-week treatment extension) of the study. This includes topical agents with substantial systemic exposure and systemic effects. After the Randomized Phase (Day 1 to Week 48 plus a 4-week treatment extension), immunomodulators may be administered after discussion and agreement with the study medical monitor
- HCV therapy during the study is prohibited
- Chronic use of systemic (oral or parenteral) glucocorticoids should be avoided; however, short treatment courses of 30 days or less (e.g., for treatment of IRIS), replacement therapy (e.g., for Addison's Disease), and topical, inhaled, or intranasal use of glucocorticosteroid will be allowed

5.6.3. Prohibited Medications for Subjects Randomly Assigned to DTG

The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, the following medications must not be administered concurrently with DTG.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- St. John's wort (*Hypericum perforatum*)

Dofetilide and pilsicainide are prohibited as DTG may inhibit renal tubular secretion resulting in increased dofetilide/pilsicainide concentrations and potential for toxicity.

For prohibited medications related to TB therapy components, please refer to the local prescribing information for information on concurrent therapies.

For a detailed list of prohibited medications, please consult the SPM.

5.6.4. Prohibited Medications for Subjects Randomly Assigned to EFV

Efavirenz has the potential to impact the following drugs potentially requiring monitoring and dose adjustment:

- HMG-CoA reductase inhibitors are prohibited due to potential for decreased plasma concentrations; dosage should be individualized based on the goal of therapy and response.
- Methadone is prohibited due to potential for decreased plasma concentrations; subjects should be monitored for signs of withdrawal and methadone dose should be adjusted as appropriate
- Warfarin is prohibited because warfarin concentrations may be increased or decreased; international normalized ratio (INR) should be monitored and dosage should be adjusted as appropriate

5.7. Treatment After the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition whether or not ViiV/GSK is providing specific post-study treatment.

All subjects randomly assigned to receive DTG who have not prematurely discontinued from the study and who successfully complete 52 weeks of treatment will continue to have access to DTG (during the DTG OLE) until it is either locally approved and commercially available, the subject no longer derives clinical benefit, or the subject meets a protocol-defined reason for discontinuation. Investigative sites must make arrangements for provision of background NRTIs to all subjects to ensure continued

access to these medications during the DTG OLE (unless provision by the sponsor is mandated by local regulation).

Subjects randomized to the EFV arm will receive EFV through their Week 52 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access EFV and NRTIs (unless mandated by local regulation).

5.8. Treatment of Study Treatment Overdose

For this open-label study, any tablet intake exceeding the recommended daily number of tablets for study drug will be considered an overdose.

For the purposes of this study, an overdose is not an AE (refer to Section 6.4.4.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a serious AE (SAE) (see Section 6.4.4.2).

If an overdose occurs and is associated with an AE requiring action, all study drugs should be temporarily discontinued until the AE resolves. The investigator should use clinical judgment in treating overdose and also refer to the prescribing information for current ARTs, as ViiV/GSK is unable to recommend specific treatment.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Time and Events Schedule

Table 2 Time and Events Table

Procedures	Screening[a]	Randomized Phase									DTG Open-Label Extension[b]	Withdrawal	Follow-up[c]
		Week							4-week Treatment Extension	DTG Dose Switch (2 weeks post TB treatment completion)			
		Day 1	4	8	12	24	36	48	52	May occur any time after the 12 week visit	Week 60 and every 12 weeks thereafter		
Clinical and other assessments													
Written informed consent	X												
Subject demography	X												
Document pulmonary, pleural, or LN TB diagnosis[d]	X												
Document pre-TB treatment MTB culture result (e.g., sputum, LN, or pleural aspirate)[e]	X	X											
Document pre-TB treatment sputum smear results, if available	X												
Perform GeneXpert or equivalent and/or Document GeneXpert or equivalent RIF-sensitive MTB	X												

Procedures	**Screening[a]**	**Randomized Phase**									**DTG Open-Label Extension[b]**	**Withdrawal**	**Follow-up[c]**
		Week							**4-week Treatment Extension**	**DTG Dose Switch (2 weeks post TB treatment completion)**			
		Day 1	**4**	**8**	**12**	**24**	**36**	**48**	**52**	**May occur any time after the 12 week visit**	**Week 60 and every 12 weeks thereafter**		
Document the subject is on a RIF-containing first-line TB treatment and record TB regimen components	X[f]												
Record pre-specified TB regimen duration	X												
Documentation of TB regimen start date	X												
Inclusion/Exclusion criteria[f]	X	X											
Prior ART history	X												
Medical history[g]		X											
CDC HIV-1 classification	X	X											
Physical examination[h]	X	X	X	X	X	X	X	X	X		X	X	X
Body weight and height		X											
Current medical conditions		X											
Cardiovascular risk assessment[i]		X											
Concomitant medication	X	X	X	X	X	X	X	X	X		X	X	X
HIV associated conditions			X	X	X	X	X	X	X		X	X	
Columbia Suicidality Severity Rating Scale[j]		X[j]	X	X	X	X	X	X	X		X	X	
Adverse events		X	X	X	X	X	X	X	X		X	X	X
SAEs	X[k]	X	X	X	X	X	X	X	X		X	X	X

Procedures	**Screening[a]**	**Randomized Phase**									**DTG Open-Label Extension[b]**	**Withdrawal**	**Follow-up[c]**
		Week							**4-week Treatment Extension**	**DTG Dose Switch (2 weeks post TB treatment completion)**			
		Day 1	**4**	**8**	**12**	**24**	**36**	**48**	**52**	**May occur any time after the 12 week visit**	**Week 60 and every 12 weeks thereafter**		
TB-associated IRIS assessment[l]			X	X	X								
Laboratory assessments													
Quantitative plasma HIV-1 RNA PCR	X	X	X	X	X	X	X	X	X[m]		X	X	
Lymphocyte subsets	X	X	X	X	X	X	X	X	X		X	X	
Plasma for storage[n]	X	X	X	X	X	X	X	X	X		X	X	
Plasma for HIV genotyping	X												
HLA-B 5701* testing[o]	X												
Clinical chemistry	X	X	X	X	X	X	X	X	X		X	X	X
Hematology	X	X	X	X	X	X	X	X	X		X	X	X
PT/INR	X												
Fasting lipids and glucose[p]		X				X		X					
Pregnancy test[q,r]	S	U	S	S	S	S	S	S	S		S	S	
HBsAg and hepatitis C (anti-HCV Ab)	X												
Pharmacogenetic sample[s]		X											
Pharmacokinetic plasma sample[t]				X		X	X	X					
Dispense PK dosing diary card			X		X	X	X			X[u]			

Procedures	Screening[a]	Randomized Phase									DTG Open-Label Extension[b]	Withdrawal	Follow-up[c]
		Week							4-week Treatment Extension	DTG Dose Switch (2 weeks post TB treatment completion)			
		Day 1	4	8	12	24	36	48	52	May occur any time after the 12 week visit	Week 60 and every 12 weeks thereafter		
Investigational product													
IVRS	X	X	X	X	X	X	X	X	X	X[v]	X	X	X
Dispense IP		X	X	X	X	X	X	X	X[v]	X	X[vw]		
IP accountability (pill counts)			X	X	X	X	X	X	X	X	X	X	

ART = antiretroviral therapy; CDC = Centers for Disease Control; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus-1; HLA-B = human leukocyte antigen-B; INR = international normalized ratio; IP = investigational product; IVRS = interactive voice response system; LN = lymph node; MTB = *Mycobacterium tuberculosis*; PCR = polymerase chain reaction; PT = prothrombin time; RIF = rifampicin; RNA = ribonucleic acid; SAE = serious adverse event; TB = tuberculosis

a. The 14-day Screening Period may be extended to 28 days. Randomization may occur as soon as all Screening results are available and up to 8 weeks after TB treatment initiation
b. Subjects randomly assigned to the DTG arm and complete the Randomized Phase through the Week 52 visit will enter into the DTG OLE. Subjects completing the DTG OLE must return to the clinic when transitioning to commercial supplies for an end of OLE visit. Study assessments will be conducted as specified for the withdrawal visit.
c. A Follow-up visit will be conducted 4 weeks after the last dose of study provided IP and is required only if a subject has ongoing AEs or laboratory abnormalities at the last on-study visit. The assessments performed should reflect what is considered medically necessary to assess the event(s).
d. Smear positive or culture positive, including sample source recorded in eCRF.
e. Results may be documented any time between Screening and Day 1.
f. Inclusion/exclusion criteria will be fully assessed at the Screening visit (to include Karnofsky assessment). Changes between the screening visit and the Day 1 visit should be assessed to ensure eligibility, including additional assessments performed at Day 1.
g. Full medical history will be collected. Targeted medical history assessments will include cardiovascular, gastrointestinal (e.g., GI bleeding, PUD), metabolic (e.g., Type I or II DM), psychiatric (e.g. depression), renal (e.g. nephrolithiasis, nephropathy, renal failure) and neurological disorders.
h. Limited physical examination to include blood pressure at Baseline (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
i. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease.
j. The Columbia-Suicidality Severity Rating Scale (subject completed questionnaire) is to be administered if a validated version in the appropriate language is available for the subject. The assessment will be performed only in countries where the validated questionnaire exists in the appropriate language. On Day 1, the questionnaire should be

completed prior to randomization.

k. Only SAEs related to study participation or to a concomitantly administered GSK/ViiV product will be collected between obtaining informed consent and administration of IP at Day 1.
l. TB-associated IRIS criteria are described in Section 6.4.6; if any of the major and/or minor criteria are identified they will be captured and reported as AEs. Toxicity management related to TB-associated IRIS cases are described in Section 6.4.3.3.
m. Quantitative plasma HIV-1 RNA are **ONLY** for subjects who had HIV-1 RNA >50 c/mL at the Week 48 visit.
n. Plasma samples for storage will be collected at each visit for possible future analyses (including but not limited to HIV-1 RNA genotypic and phenotypic analyses, HIV-1 RNA levels, and immunological parameters). These samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable. Plasma for storage sample should also be collected at the unscheduled visit for retesting suspected virologic withdrawal. Additionally, for genotypic and phenotypic resistance analyses baseline samples from all subjects will be used and later samples in cases of confirmed virologic withdrawal criteria met (for paired baseline and endpoint genotypes).
o. Subjects starting ABC as one of the NRTIs must have been screened and be negative for the *HLA-B*5701* allele.
p. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
q. Pregnancy testing will be conducted (women of childbearing potential only) on serum samples with the exception of Day 1, which must be a urine test to confirm status prior to administration of IP.
r. Remind females of reproductive potential of the need to avoid pregnancy while in the study and adherence to the study's contraceptive requirements.
s. Informed consent for optional pharmacogenetics (PGx) research must be obtained before collecting a sample. Collection of the PGx sample at Day 1 is preferred; however, this sample may be collected at any time during the study.
t. For subjects randomly assigned to EFV, mid-dosing interval samples will be collected at Weeks 8, 24, 36, and 48. For subjects randomly assigned to DTG, 1 sample each for pre-dose, 1 to 3 hours post-dose, 4 to 12 hours post-dose will be collected at Weeks 8 and 36, and 1 sample pre-dose will be collected at Weeks 24 and 48. If PK sampling is not performed the visit will be rescheduled to collect the PK sample and if applicable the subject will be provided a new diary card. Instructions on PK sample collection are described in Section 6.5.2. Blood samples should be collected into K2EDTA tubes.
u. Collect DTG twice daily PK diary card and provide the subject with the DTG once daily PK diary card.
v. The IVRS will capture the point at which the subject is within 2 weeks of completing their TB treatment and the site will notify the subject to return to the clinic for the DTG switch visit in order to dispense the DTG 50 mg once daily dose.
w. For subjects receiving DTG during the DTG OLE only.

6.1.1. TB Time and Events Schedule

Table 3 TB Time and Events Table

Procedures	TB Treatment Intensive Phase		TB Treatment Continuation Phase		
	Baseline	Month 2	Month 4	Month 6	Month 9
Laboratory assessments					
Collection of sputum samples for MTB smear and culture testing[a]	X	X	X	X	X
TB regimen assessments					
TB medications[b]	X	X	X	X	X
TB treatment interruptions[c]		X	X	X	X
TB treatment re-introduction[d]		X	X	X	X
Document RIF-sensitivity[e]	X	X	X	X	X

MTB = *Mycobacterium tuberculosis*, TB = tuberculosis

a. To be performed at the local laboratory. The laboratory and method for that subject should remain the same throughout the study. Results of testing will be recorded in the eCRF. Sputum does not need to be collected from subjects with pleural or lymph node TB who do not also have pulmonary TB. If subjects are no longer producing sputum at 4 months, 6 months, and 9 months and no sputum sample can therefore be collected, then this fact must be recorded in the eCRF. Subjects who complete their TB treatment at 6 months, do not require a sputum sample to be collected at 9 months, unless clinically indicated (investigator decision).
b. Record all TB treatment medications taken during the intensive and continuation phases on the TB treatment medication eCRF.
c. Any missed doses or changes to the regimen should be recorded on the TB treatment medication eCRF. If the TB regimen is interrupted for more than 14 days, the subject must be withdrawn from the study.
d. Re-introduction guidelines are described in Section 6.4.3.1.1.
e. Rifampicin susceptibility testing at baseline is mandatory. The investigator may repeat RIF susceptibility testing at other times, as clinically indicated. If at any time, an isolate is found to be RIF-resistant, then the subject must be withdrawn from the study.

6.2. Critical Baseline Assessments

Written informed consent must be obtained from each potentially eligible subject (or his/her legal representative) by study site personnel prior to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the IRB/IEC. After signing an informed consent, subjects will complete Screening assessments to determine subject eligibility. Each subject being screened for study enrollment evaluation will be assigned a subject number at the Screening visit. This number will be given sequentially in chronological order of subject presentation according to a numeric roster provided by PPD.

6.2.1. Screening Assessments

Assessments to be conducted at Screening are provided in the Time and Events schedule (Table 2).

All subjects will complete the Screening Period approximately 14 days prior to Baseline (Day 1) during which time all clinical and laboratory assessments of eligibility must be performed and reviewed. The Screening Period may be extended to 28 days to

accommodate availability of all Screening assessment results and scheduling. All Screening results must be available prior to randomization.

Eligibility criteria must be carefully assessed at the Screening visit. Physical examinations should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Smear-positive sample, site from which sample was obtained (e.g., sputum, LN, or pleural aspirate) and sputum smear grade result, culture date of collection and result (if available), results of Gene Xpert test, including RIF genotypic susceptibility testing will be recorded at the Screening visit.

Subjects who meet all entry criteria are randomly assigned to treatment and assigned a randomization number. Subjects not meeting all inclusion and exclusion criteria at the initial screen may be rescreened **only once** and the subject will receive a new subject number at that time. With the exception of a disqualifying viral genotype or documentation of RIF resistance, a single repeat test (re-test) per analyte or assessment is allowed during the Screening Period to determine eligibility. Subjects who are randomized into the study and subsequently withdrawn from the study for any reason may not be rescreened.

Note: Where *HLA-B*5701* screening is considered standard of care, it is recommended that investigators screen for presence of the *HLA-B*5701* allele in any subject for whom an ABC-containing product (e.g., ZIAGEN™, EPZICOM™, KIVEXA™) may be considered as part of background regimen and *HLA-B*5701* status is unknown (even if the subject has previously tolerated ABC). **Use of ABC in subjects known to carry *HLA-B*5701* is not recommended** and should be considered only under exceptional circumstances where potential benefit outweighs the risk and only under close medical supervision.

6.2.2. Baseline Assessments (Day 1)

Assessments to be conducted at Baseline (Day 1) are provided in the Time and Events schedule (Table 2).

At Day 1 and prior to randomization, any changes to the eligibility parameters must be assessed and any results required prior to randomization (e.g., Day 1 urine pregnancy test for women of childbearing potential) must be available and reviewed.

Cardiovascular risk factors will be assessed at Baseline and assessments will include smoking status and history and family history of cardiac events.

For subjects who agree to the optional assessment, a whole blood sample for pharmacogenetic (PGx) research should be collected at Day 1; however this sample may be collected at any time during the study (see Section 11.1).

6.3. Efficacy

6.3.1. Efficacy Evaluations

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events Table (Table 2). Methods to be used may include but are not limited to the Abbott Realtime HIV-1 Assay with lower limit of detection (LLOD) 40 c/mL. In some cases (e.g., where the HIV-1 RNA is below the LLOD for a given assay) additional exploratory methods may be used to further characterize plasma HIV-1 RNA levels.

Lymphocyte Subsets

Blood samples will be collected for assessment of lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ lymphocyte counts) according to the Time and Events Table (Table 2).

Sputum MTB Cultures

Sputum samples will be collected for assessment of positive TB cultures according to the TB Time and Events Table (Table 3). TB cultures are to be performed locally and results will be collected in the eCRF.

CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the Time and Events Table (Table 2). HIV associated conditions will be assessed according to the 1993 CDC Revised Classification System for HIV Infection in Adults (see Section 11.2). Indicators of clinical disease progression are defined as:

CDC Category A at enrollment→ Category B event;

CDC Category A at enrollment→ Category C event;

CDC Category B at enrollment→ Category C event;

CDC Category C at enrollment→ New Category C Event;

CDC Category A, B or C at enrollment→ Death

6.3.2. Primary Efficacy Endpoint

The primary endpoint will be the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population in the DTG arm. This endpoint will also be evaluated in the modified ITT-E (MITT-E) population.

6.3.3. Secondary Efficacy Endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the EFV arm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related AE, safety stopping criteria, or lack of efficacy);
- Changes from baseline in CD4+ counts at Week 24 and Week 48.

6.3.4. Tertiary Efficacy Endpoints

- Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses and death);
- Proportion of subjects with TB treatment success (using the WHO definition, to be detailed in the reporting and analysis plan [RAP]);
- Proportion of subjects with pulmonary MTB who are sputum culture-negative 2 months after starting TB treatment.

6.4. Safety

Safety assessments will be conducted according to the Time and Events Table (Table 2) and will include the following:

- Monitoring and recording all AEs and SAEs. Additional information on the time period and frequency of detecting AEs and SAEs is provided in Section 6.4.12;
- Regular monitoring of hematology and blood chemistry parameters;
- Periodic assessment of fasting lipids and glucose;
- Physical examinations should be conducted as part of normal routine clinical care but will not be entered systematically in the eCRF. Abnormalities noted during any examination must be recorded in the eCRF (e.g., in the current medical conditions or AE logs);
- Evaluation and documentation of all concomitant medications and blood products received;
- Suicidality monitoring using the Columbia-Suicide Severity Rating Scale (C-SSRS; Section 6.4.10).

Any appropriately qualified site personnel (e.g., investigator, sub-investigator, or study coordinator/nurse) can perform assessments. With the exception of TB culture, a central laboratory chosen by GSK/ViiV will undertake all routine scheduled laboratory evaluations within the study. Refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipping for each laboratory test.

Table 4 Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[b]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine[c]
PT/INR[d]			
Fasting Lipid Panel[e]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			
Plasma HIV-1 RNA			
CD4+ cell counts			
Hepatitis B (HBsAg) and hepatitis C (anti-HCV Ab)[d]			
Pregnancy test for women of childbearing potential[f]			
*HLA-B*5701* screening[d]			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

a. Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b. Fasting glucose will be collected at Day 1 and Weeks, 24, and 48 during the study. For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
c. Glomerular filtration rate (GFR) will be estimated by the central laboratory using the CKD-EPI formula using serum creatinine [Inker, 2012].
d. Screening visit only
e. For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
f. Urine pregnancy test and serum pregnancy test will be performed according to Table 2.

6.4.1. Safety Endpoints

- Incidence and severity of all AEs, SAEs, and laboratory abnormalities;
- Proportion of subjects who permanently discontinue IP or TB treatment due to AEs or death;
- Proportion of subjects who temporarily discontinue IP and/or TB therapy due to AEs;
- Proportion of subjects with TB-associated IRIS

  Note: the clinical team will review the AE terms and HIV conditions in order to identify TB-associated IRIS cases. TB-associated IRIS criteria are described in Section 6.4.6 and toxicity management for TB-associated IRIS cases are described in Section 6.4.3.3.

6.4.2. Toxicity Management

Adverse events that occur during the study should be evaluated by the investigator and graded according to the Division of AIDS (DAIDS) toxicity scales (see Section 11.3). Additional information regarding detecting, documenting, and reporting AEs and SAEs are available in Section 6.4.3.9.

Investigational product may be interrupted at the discretion of the investigator and according to the severity of the AE. If one or more antiretroviral drugs are held due to toxicity or AEs, generally, all antiretroviral drugs should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each antiretroviral drug of the regimen. In some cases (e.g., EFV), short continuation of the dual NRTI components of the regimen after interruption of the third antiretroviral drug may be appropriate in order to minimize the risk of development of resistance.

No toxicity-related dose reductions of IP will be allowed. Investigational product should be restarted as soon as medically appropriate; in general, this should be no longer than 4 weeks after interruption (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of IP or temporary interruption of one or more but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Guidance is provided below on subject management and IP interruptions based on the severity of the AE; for specific toxicities, please refer to Section 6.4.3. All changes in IP must be accurately recorded in the subject's eCRF.

When possible, concomitant medications (like TB treatment components) should be held first at the discretion of the principal investigator if he/she suspects they are contributing to the toxicity

Toxicities That the Investigator Considers Related or Possibly Related to TB Treatment

Toxicities that the investigator considers related or possibly related to TB treatment should be managed with reference to applicable product labeling and local guidelines.

Note: In instances where both IP and TB treatments are interrupted due to either a clinical or laboratory toxicity, and it is decided to re-introduce these agents e.g., upon event improvement or resolution (following consultation with the medical monitor for Grade 3 toxicities), the TB treatment should be restarted first according to Section 11.6, followed by trimethoprim-sulfamethoxazole (TMP-SMX), and then ART.

Toxicities That the Investigator Considers Related or Possibly Related to one or More NRTIs

Toxicities that the investigator considers related or possibly related to one of the background NRTIs may be addressed by substitution of the medication for another approved NRTI one time during the study (Section 5.1.5). In addition, toxicities that the

investigator considers related or possibly related to any NRTI should be managed with reference to applicable product labeling.

Note: For subjects receiving an ABC-containing product as part of the background regimen, in the event of a discontinuation of ABC for any reason, reinitiation of this drug should be undertaken with caution. The investigator should obtain a complete history of the events surrounding the discontinuation of the ABC-containing product, evaluate for the possibility of a clinically suspected hypersensitivity reaction (HSR), and initiate subject management as outlined in the local country prescribing information, regardless of a subject's *HLA-B*5701* status. Screening for the presence of *HLA-B*5701* is recommended prior to reinitiating treatment with ABC-containing products in subjects of unknown *HLA-B*5701* status who have previously tolerated ABC.

Grade 1 or Grade 2 Toxicity/Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE or toxicity may continue IP at the discretion of the investigator. For exceptions to this guideline see Section 6.4.3.

Subjects who voluntarily decide to terminate their participation in the study due to a Grade 1 or 2 AE should complete the Withdrawal and Follow-up visit.

Grade 3 Toxicity/Adverse Event

Subjects who develop a Grade 3 AE or Grade 3 toxicity should be managed as follows:

If the investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by IP, dosing may continue after discussion with the medical monitor.

Subjects who develop a Grade 3 AE or toxicity that the investigator considers related or possibly related to the IP should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, IP may be restarted.

Should the same Grade 3 AE recur within 28 days in the same subject, the IP should be permanently discontinued and the subject withdrawn from study. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to complete the Withdrawal visit. A Follow-up visit should be performed 4 weeks after the last dose of IP.

Subjects with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug-related causes, and, following discussion with the medical monitor, may continue IP if the investigator has compelling evidence that the toxicity is not related to IP.

Exceptions are noted for lipid abnormalities in Section 6.4.3.6.

Grade 4 Toxicity/Adverse Event

Subjects who develop a Grade 4 AE or toxicity should have IP permanently discontinued. However, if the investigator has compelling evidence that the AE is not causally related to the IP, dosing may continue after discussion with and assent from the medical monitor. Subjects should be rechecked each week until the AE returns to Grade 2.

Subjects experiencing Grade 4 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and are encouraged to complete the Withdrawal and Follow-up visit as noted above.

Subjects with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue therapy if the investigator has compelling evidence that the toxicity is not related to IP. Exceptions are noted for lipid abnormalities in Section 6.4.3.6. A Follow-up visit should be performed 4 weeks after the last dose of IP if AEs or laboratory abnormalities are ongoing.

6.4.3. Specific Toxicity Management

General guidelines are described below for the management of specific toxicities that are considered to be related or possibly related to IP, background NRTIs, and TB treatment and include the following:

- Liver chemistry stopping and follow-up criteria (Section 6.4.3.1)
- IRIS (Section 6.4.3.3)
- Decline in renal function (Section 6.4.3.4)
- Allergic reaction (Section 6.4.3.5)
- Hypertriglyceridemia/hypercholesterolemia (Section 6.4.3.6)
- Creatine phosphokinase (CPK) elevation (Section 6.4.3.7)
- Rash (Section 6.4.3.8)
- Petechial rash due to RIF-induced thrombocytopenia (Section 6.4.3.9)

Subjects who permanently discontinue IP for reasons of toxicity should be followed weekly until resolution or stabilization of the AE and encouraged to complete the withdrawal and Follow-Up study evaluations as noted above.

6.4.3.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of IP and the Follow-up period. If ALT >2 × ULN, liver chemistries should be monitored weekly for 2 weeks, then every 2 weeks thereafter until normalized.

While receiving IP co-administered with TB treatment, both will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin; bilirubin fractionation required)
    - NOTE: Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event meets liver stopping criteria;
- ALT ≥3 × ULN with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR
- ALT ≥5 × ULN; regardless of symptoms

After completion of TB treatment, while receiving IP, ART will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin; bilirubin fractionation required)
    - NOTE: Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event meets liver stopping criteria;
- ALT ≥3 × ULN (if baseline ALT is <ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR
- ALT ≥3 × baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥ 5 × ULN and <8 × ULN (after TB treatment is complete) that persists ≥2 weeks (with bilirubin <2 × ULN and no signs or symptoms of acute hepatitis or hypersensitivity); ALT ≥5 × ULN but <8 × ULN (after TB treatment is complete) and cannot be monitored weekly for >2 weeks; and subjects who develop ALT ≥5 × ULN should be followed weekly until resolution or stabilization (ALT <5 × ULN on 2 consecutive evaluations);
- ALT > 8 × ULN; regardless of symptoms.

When liver chemistry stopping criteria are met, do the following:

- Immediately hold IP;
- According to guidelines, isoniazid, pyrazinamide, RIF, and TMP-SMX should be stopped simultaneously (when applicable) with the interruption of the ART;
- Report the event to the medical monitor within 24 hours of learning its occurrence (see Table 7 and Section 6.4.14);

- Complete the liver event and SAE eCRFs, where applicable, (see Section 6.4.14);
- Complete the liver imaging, liver biopsy, or both eCRFs if these tests are performed;
- Perform liver event follow-up assessments (described in this section), and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below;
- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow-up assessments (described in this section), and close monitoring;
- A specialist or hepatology consultation is recommended;
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase, and bilirubin) resolve, stabilize, or return to within baseline values;

Make every attempt to carry out the liver event follow-up assessments described below:

- Viral hepatitis serology including:
- Hepatitis A IgM antibody;
- HBsAg and hepatitis B core antibody (IgM);
- Hepatitis C RNA;
- Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Blood sample for PK analysis, obtained within 60 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of IP prior to blood draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM;
- Serum acetaminophen test (APAP adduct test). Please refer to the SPM and Quest Diagnostics Laboratory manual for further details;
- Serum CPK and lactate dehydrogenase;
- Fractionate bilirubin, if total bilirubin is ≥1.5 × ULN;
- Obtain complete blood count with differential to assess eosinophilia;
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;

- Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form. Record alcohol use on the liver event alcohol intake case report form.

6.4.3.1.1. Alternate RIF-Containing TB Treatment Regimen and Bridging Regimen

In cases of TB treatment interruption due to hepatotoxicity, until the cause of the hepatotoxicity is identified it may be necessary to treat the subject's tuberculosis with a bridging non-RIF–containing anti-tuberculosis regimen with low risk of hepatotoxicity. Drugs that may be used include (i) ethambutol, (ii) an injectable: e.g., aminoglycoside (such as streptomycin, amikacin, and kanamycin) or capreomycin or (iii) a fluoroquinolone (e.g., moxifloxacin or levofloxacin). A bridging regimen should be used to avoid reaching the 14-day treatment interruption limit and therefore avoid having to withdraw a study subject from the study.

Both CDC and BHIVA guidelines recommend that patients be treated with two or more active drugs drawn from each of the groups listed (i) to (iii) above (i.e., ethambutol and streptomycin, or ethambutol and moxifloxacin) while waiting for standard therapy to be reintroduced in consultation with a local expert. A note for caution comes from reports of severe hepatotoxicity with moxifloxacin.

Tuberculosis treatment may be re-introduced when ALT <2 × ULN. Suggested re-introduction regimen schedules after TB treatment interruption are provided in Table 5 and Table 6, which describe options excluding ethambutol (12) or isoniazid (13) for testing re-exposure to TB drugs, respectively. TB treatment should be restarted first [BHIVA Guidelines, 2011], followed by TMP-SMX, if required for patient care, followed by ART. Daily monitoring of the patient's condition and liver chemistries (ALT, AST, total bilirubin, alkaline phosphatase) is required during the reintroduction. Guidance from a local expert should be sought.

The time on the standard regimen (i.e., the initial WHO first-line TB regimen) should count towards time on the acceptable alternate RIF-containing TB treatment, provided the treatment interruption was no longer than 14 days [CDC 2003 Guidelines]. Only time on full-dose of the WHO first-line regimen or listed in Section 11.6 counts towards time on a TB regimen. Time on partial doses of TB drugs as part of the reintroduction does not count, but time on the bridging regimen does count. Further information on alternate RIF-containing TB treatment regimens are described in Section 11.6.

Table 5 Re-Introduction Guidelines for Regimen 1

Day	Rifampicin	Isoniazid	Pyrazinamide
1		50 mg	
2		150 mg	
3		full dose	
4	75 mg	full dose	
5	150 mg	full dose	
6	300 mg	full dose	
7	full dose	full dose	
8	full dose	full dose	250 mg
9	full dose	full dose	500 mg
10	full dose	full dose	1 g
11	full dose	full dose	full dose
12	full dose	full dose	full dose
13	full dose	full dose	full dose

kg = kilogram; mg = milligram; g = gram

Table 6 Re-Introduction Guidelines for Regimen 2

Day	Rifampicin	Ethambutol	Pyrazinamide
1	75 mg		
2	150 mg		
3	300 mg		
4	450 mg <50 kg or 600 mg >50 kg		
5	450 mg/600 mg	5 mg/kg	
6	450 mg/600 mg	10 mg/kg	
7	450 mg/600 mg	15 mg/kg	
8	450 mg/600 mg	15 mg/kg	250 mg
9	450 mg/600 mg	15 mg/kg	500 mg
10	450 mg/600 mg	15 mg/kg	1 g
11	450 mg/600 mg	15 mg/kg	1.5 g <50 kg or 2 g >50 kg
12	450 mg/600 mg	15 mg/kg	1.5 g/2 g

kg = kilogram; mg = milligram; g = gram

6.4.3.2. Restarting Investigational Product

Drug restart/rechallenge following liver events that are possibly related to IP

Liver toxicity in the setting of concomitant TB treatment and ART is most commonly related to the antituberculosis medications rather than the HIV medications. As described above, TB treatment (isoniazid, RIF, and pyrazinamide) should all be discontinued (Section 11.6 for alternate TB therapy recommendations), along with all antiretrovirals and TMP-SMX, if being administered, when liver stopping criteria are met. In some cases (e.g., EFV), short continuation of the dual NRTI components of the regimen after interruption of the third antiretroviral drug may be appropriate in order to minimize the risk of development of resistance. Liver chemistries should be followed at least twice weekly until they have returned to <2 × ULN. Re-introduction of TB treatment should then be undertaken first as described in Section 11.6, followed by TMP-SMX, and then ART should be restarted.

If liver toxicity is due to TB treatment and an alternative anti-TB treatment containing RIF can be successfully introduced, the authorization for restarting the IP may be discussed between the investigator and the study medical monitor, without the need for approval from the ViiV Safety and Labeling Committee (VSLC) (see details in Section 11.5). If liver toxicity is not due to TB treatment, the case will need VSLC approval to restart DTG (this approval can be ad hoc).

For Grade 4 ALT elevations (≥10 × ULN) it is recommended that the subject not be rechallenged with pyrazinamide. Alternate RIF-containing TB treatment regimens are described in Section 11.6 [BHIVA Guidelines Section 7.2, 2011 and CDC, 2003 Section 8.8.2].

The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.

Subjects approved by ViiV/GSK for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for 1 month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol.

Refer to Section 11.5 for further details.

Drug restart following transient resolving liver events not related to IP

Refer to Section 11.5 for further details.

6.4.3.3. TB-Associated IRIS Toxicity Management

Subjects presenting with Grade 3 (except Grade 3 TB-associated IRIS toxicity manifested only by respiratory signs and symptoms) and Grade 4 TB-associated IRIS toxicity should have the IP withheld and be rechecked each week until the AE returns to Grade ≤2. Once the AE is Grade ≤2, IP may be restarted.

Grade 3 TB-associated IRIS toxicity restricted to respiratory signs and symptoms may be managed by the investigator including, but not limited to, assessment of treatment failure and therapy with steroids, for a period of 1 week without having the IP withheld. After this period, if the event persists as a Grade 3 event, withholding the IP and having weekly follow-ups until the AE returns to Grade ≤2 would be required.

6.4.3.4. Decline in Renal Function

Subjects who experience an increase in creatinine from Baseline of 45 µMol/L (or 0.5 mg/dL) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine ratio should be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

Subjects who have a decline in estimated GFR (using the CKD-EPI method) of >50% must return for a confirmatory creatinine assessment as soon as possible. A urinalysis and

urine albumin/creatinine ratio should be done at this confirmatory visit. If the estimated GFR has declined by >50% (confirmed), then IP should be withheld and the investigator should contact the study medical monitor to discuss the rationale for restarting IP (if appropriate). Consideration for confounding factors (e.g., other medications, dehydration, concurrent medications) should be taken into account and a nephrology consult may be obtained. If a subject is also receiving TDF, then a switch to an alternate NRTI should be considered if restarting IP. One background NRTI change is allowed for management of drug toxicity as described in Section 5.1.5. If IP is not reinitiated the subject must be withdrawn.

6.4.3.5. Allergic Reaction

Grade 1 or 2: Subjects may continue IP at the discretion of the investigator. The subject should be advised to contact the investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Grade ≥3: Subjects with allergic reactions that are considered to be possibly or probably related to the IP should permanently discontinue the IP regimen and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

Allergic reactions that the investigator considers related or possibly related to TB treatment should be managed with reference to applicable product labeling, local guidelines and, where the re-introduction of TB treatment is applicable, the recommendations outlined in Section 11.6.

Subjects receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information.

6.4.3.6. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Time and Events Table (Table 2). Subjects who experience asymptomatic triglyceride or cholesterol elevations may continue to receive IP.

6.4.3.7. Creatine Phosphokinase Elevation

Grade ≥3: Subjects with an elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment.

Grade 4: Subjects with an elevation in CPK should have a repeat assessment after the subject has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the IP, IP should be discontinued and the subject withdrawn from the study.

A history regarding use of drugs known to cause an increase in CPK (such as statins) and physical activity or exercise preceding the CPK evaluation should be obtained.

6.4.3.8. Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first 10 weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within 2 to 3 weeks. No instances of serious skin reaction, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, have been reported for DTG in clinical trials. Additional information on characterization of HSR and rash observed with DTG-containing ART is in the current version of the IB [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01]]. Approximately one-fourth of adult subjects treated with EFV in clinical studies presented rash of any grade, with rare cases (<1%) being Grade 3 or higher. For information on rashes observed in EFV treated subjects refer to EFV product information [Sustiva (efavirenz) US Product Information, May 2013; Sustiva Package Insert, 2013; Sustiva Summary of Product Information, 2014].

TB treatment regimens commonly cause rashes that are typically mild/moderate in severity and usually start within the first 2 months of treatment initiation. Mild rashes without mucosal involvement can be treated symptomatically. More widespread worsening rashes or those with systemic symptoms require all drug cessation. It is recommended that when TB drugs, HIV drugs, and TMP-SMX are interrupted concomitantly due to treatment emerging rash that TB drugs be reintroduced first, then TMP-SMX, and finally the ART, in a similar regimen as the one suggested for hepatotoxicity management (Section 6.4.3.1.1).

Grade 1: Subjects with an isolated Grade 1 rash may continue IP at the investigator's discretion. The subject should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Grade 2: Subjects may continue IP for an isolated Grade 2 rash. However, IP (and all other concurrent medication(s) suspected in the investigators causality assessment including TB treatment medications) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT (see Section 6.4.3.1). The subject should be advised to contact the physician immediately if rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Grade 3 or 4: Subjects should permanently discontinue IP (and all other concurrent medication(s) suspected in the investigators causality assessment should be interrupted) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

The rash and any associated symptoms should be reported as AEs (see Section 6.4.3.9) and appropriate toxicity ratings should be used to grade the events (see Section 11.3).

If the etiology of the rash can be definitely diagnosed as being unrelated to IP and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

A rash that the investigator considers related or possibly related to TB treatment should be managed with reference to applicable product labeling, local guidelines and, where the re-introduction of TB treatment is applicable, the recommendations outlined in Section 11.6.

Subjects receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information. In any subject treated with ABC, the clinical diagnosis of suspected HSR must remain the basis of clinical decision making. Regardless of HLA-B*5701 status, it is important to permanently discontinue ABC and not re-challenge with ABC (i.e., ABC/DTG/3TC, Ziagen, EPZICOM/KIVEXA, or TRIZIVIR™), if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

6.4.3.9. Petechial Rash

Thrombocytopenia induced by RIF and manifested by petechial rash has been described with high-dose intermittent therapy and also after resumption of interrupted treatment. As this event is reversible and potentially serious, RIF should be immediately and permanently withdrawn. This would also require discontinuation from the study, as the subject must be on a RIF-containing TB treatment regimen.

6.4.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

6.4.4.1. Definition of an AE

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study

- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE or SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

6.4.4.2. Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life threatening

NOTE: The term "life threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct) (or ALT ≥3 × ULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

Note: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.4.5. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

Additionally, diagnostic test results that represent a sign of a clinical condition that is already reported as an AE need not be reported as this would be redundant.

6.4.6. TB-Associated Immune Reconstitution Inflammatory Syndrome

The assessment of the frequency of TB-associated IRIS is one of the secondary study objectives (Section 2.2). In order to achieve this goal, investigators need to carefully

document and manage signs and symptoms that could be related to TB-associated IRIS. In addition, the clinical team will review the AE terms and HIV conditions in order to identify TB-associated IRIS cases. Information on X-ray findings and repeat sputum culture and susceptibility testing may be helpful in distinguishing IRIS from worsening TB disease or development of TB resistance.

This section provides guidance on criteria for TB-associated IRIS diagnosis during the study. TB-associated IRIS assessments will be performed according to the Time and Events schedule (Table 3). If any of the major and/or minor criteria described in this section occur, they should be captured and reported as AEs.

Details on toxicity management for TB-associated IRIS cases are described in Section 6.4.3.3.

IRIS is associated with the initiation of highly active ART for subjects co-infected with HIV-1 and TB. IRIS appears to be associated with severe immunosuppression, the speed of immune reconstitution, and TB severity. The diagnosis of this syndrome is actually a diagnosis of exclusion, after ruling out other diagnoses such as non-response to treatment (including failure to TB treatment due to drug resistance), poor adherence to TB treatment, recurrence of TB, toxicity or drug reaction, neoplasia, and opportunistic infections or other causes of fever. In biological terms, the IRIS could be associated with a burst of specific Th1 CD4+ T cells to tuberculin purified protein derivative, detectable by ELISPOT for IFN-γ.

There are 3 components of the existing case definition for paradoxical TB-associated IRIS [Meintjes, 2008]:

a. Preliminary Requirements

Both of the following requirements must be met:

- Diagnosis of TB, meeting WHO criteria for the diagnosis of either positive or negative sputum smear-positive pulmonary TB or extrapulmonary TB before starting the ART
- Initial response to TB treatment: the subject's condition should be stabilized or improved in the presence of appropriate treatment for TB before starting the ART (e.g., remission of night sweats, fever, cough, weight loss). (Note: This does not apply to subjects starting ART within the first 2 weeks of TB treatment, since this is not sufficient time for the occurrence of clinical response)

b. Clinical Criteria

The onset of IRIS signs and symptoms related to TB should occur within the first 3 months of starting, restarting, or changing the ART regimen for treatment failure.

At least 1 major criterion or 2 of the minor criteria listed below must be present:

Major criteria

- New lymph nodes or increase in existing lymph nodes, cold abscesses, or other focal tissue involvement (e.g., tuberculous arthritis)

- New x-ray findings suggestive of TB or worsening of existing images (e.g. chest x-ray, abdominal ultrasonography, computed tomography or magnetic resonance imaging)
- New onset of CNS TB or worsening of existing disease (meningitis or focal neurological deficit caused by tuberculoma)
- New onset or worsening serositis (pleural effusion, ascites, or pericardial effusion)

Minor criteria

- New constitutional symptoms or worsening of existing symptoms, such as fever, night sweats, or weight loss
- New respiratory symptoms or worsening of existing symptoms such as coughing, dyspnea, or rhonchi
- Recent onset or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

6.4.7. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

This information should be recorded in the specific cardiovascular eCRF within 1 week of when the AE/SAE(s) are first reported.

6.4.8. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

6.4.9. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (see Section 11.2) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 6.4.4.2), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.

Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

6.4.10. Suicidality Monitoring

Subjects with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behavior). Therefore, it is appropriate to monitor subjects for suicidality before and during treatment. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior.

Assessment of treatment-emergent suicidality will be monitored during this study using the C-SSRS, if a validated version in the appropriate language is available for the subject. The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Oquendo, 2003]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Day 1 (Baseline) visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. The C-SSRS is to be administered as a patient-completed questionnaire specified in the Time and Events Table (Table 2). Refer to the SPM for further details on questionnaire delivery and follow-ups.

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (nonserious or SAE) eCRF form on any subject that experiences a PSRAE while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to ViiV/GSK within 1 week of the investigator diagnosing a PSRAE.

6.4.11. Pregnancy

6.4.11.1. Pregnancy Testing

Women of childbearing potential must have a negative pregnancy test at Screening and Day 1 to be eligible for administration of IP. Pregnancy testing will also be conducted according to the Time and Events Table (Table 2) and at any time during the study when pregnancy is suspected.

Additionally, a pregnancy test should also be performed prior to IP re-administration, when IP administration is disrupted for more than 7 days.

6.4.11.2. Time Period for Collecting Pregnancy Information

Information on the occurrence of pregnancies in female subjects will be collected over the period starting at Screening and ending at the final Follow-up visit. Only those pregnancies that occur following the first dose of IP will be reported to the medical monitor. Follow-up information will only be collected for pregnancies occurring from Day 1 to the final Follow-up visit.

6.4.11.3. Action to be Taken if Pregnancy Occurs

Any female who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study. Subjects using DTG must immediately discontinue the IP.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as SAEs.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to ViiV/GSK.

ViiV/GSK's central safety department will also forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

6.4.12. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff personnel are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Beginning at Day 1 and continuing until the follow-up contact, AEs will be recorded.

Serious AEs will be collected throughout the entire study. Any SAE assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV/GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to medical monitor within 24 hours, as indicated in Section 6.4.14.

6.4.13. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?”

“Have you had any (other) medical problems since your last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

6.4.14. Prompt Reporting of Serious Adverse Events and Other Events

Serious AEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to the medical monitor as described in Table 7 once the investigator determines that the event meets the protocol definition for that event.

Criteria for liver chemistry stopping and follow-up criteria are in Section 6.4.3.1.

Table 7 Reporting of Serious Adverse Events and Other Events

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow-up reports to be completed within 1 week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow-up reports to be completed within 1 week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Suspected ABC HSR[a]	1 week	ABC HSR eCRF	1 week	Updated ABC HSR eCRF
ALT≥3×ULN **and** bilirubin≥2×ULN (>35% direct) (or ALT≥3×ULN	24 hours[b]	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable[c]	24 hours	Updated "SAE" data collection tool/"Liver Event" documents[c]
ALT≥5×ULN that persists ≥2 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥8×ULN	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3×ULN or ALT ≥3 fold increase from baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]

ABC = abacavir; CV = cardiovascular; eCRF = electronic case report form; HSR = hypersensitivity reaction; SAE = serious adverse event; ULN = upper limit of normal.

a. ABC HSR eCRF required only if event meets one of the definitions in Section 6.4.4.2.
b. PPD must be contacted at onset of liver chemistry elevations to discuss subject safety.
c. Liver event documents (i.e., "Liver Event eCRF" and "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

The investigator will be required to confirm review of the SAE causality by ticking the 'For Investigators ONLY' box at the bottom of the eCRF page within 72 hours of submission of the SAE.

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.4.14.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

ViiV/GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. ViiV/GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from ViiV/GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements. Reporting of SAEs and other events to ViiV/GSK/PPD is addressed in Table 7.

6.4.14.2. Reporting of ABC Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC develops in subjects receiving ABC as part of their NRTI background regimen, and meets the definition of an SAE as described in Section 6.4.4, then, in addition to reporting the case as an SAE, the ABC HSR eCRF should also be completed within 1 week of the onset of the HSR (see Section 6.4.14).

6.4.15. Other Safety Outcomes

Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 4, must be performed by the central laboratory, Quest Diagnostics, or a laboratory contracted by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events schedule (Table 2). Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided in the Quest Diagnostic Laboratory manual. Reference ranges for all safety parameters will be provided to the site by Quest Diagnostics.

Mycobacterium TB laboratory assessments are to be performed locally and the results must be recorded in the subject's eCRF in accordance with Time and Events schedules (Table 2 and Table 3).

All study-required laboratory assessments will be performed by a central laboratory. If required for cardiovascular events, additional specific local laboratory assessments will be recorded in the specific cardiovascular eCRF (see Section 6.4.7).

6.5. Pharmacokinetics

6.5.1. Pharmacokinetic Endpoints

DTG and EFV concentrations will be evaluated at Weeks 8, 24, 36, and 48 using sparse PK sampling.

DTG and EFV drug concentrations will be analyzed using a population PK modeling approach to evaluate the effects of demographic factors (e.g., weight, age, gender, and race), subject characteristics, and on/off RIF treatment on DTG and EFV PK parameters and variability. DTG PK data obtained from this study may be combined with DTG PK data from previous Phase 3 studies for the population PK modeling. Plasma DTG and EFV PK parameters (AUC0-τ, Cmax, and Cτ) estimated by population PK modeling based on sparse PK sampling will be reported and used in the analysis of correlation with antiviral activities at Weeks 24 and 48.

6.5.2. Pharmacokinetic Sample Collection

Blood samples (2 mL each) will be collected from as many subjects as possible for evaluation of DTG and EFV plasma PK levels. Blood samples should be collected into K2EDTA tubes. The PK sampling visits will occur at Weeks 8, 24, 36, and 48 during the Randomized Phase. For the EFV arm, mid-dosing interval samples will be collected at Weeks 8, 24, 36, and 48. For the DTG arm, 1 sample will be collected for each of the following time points relative to IP dose: pre-dose, 1 to 3 hours post-dose, and 4 to 12 hours post-dose at Weeks 8 and 36 as well as 1 sample pre-dose at Weeks 24 and 48 Table 8. If PK sampling is not performed at the planned visit for any reason then the PK sample collection visit will be rescheduled within 4 weeks of the originally scheduled PK visit. The subject will be provided a new diary card at the rescheduled visit for the next PK visit, if applicable.

Table 8 Pharmacokinetic Sample Schedule

Treatment Arm	Week	Sample Times Relative to Dose
DTG PK	8 and 36	1 sample pre-dose[a] 1 sample 1 to 3 h post-dose[b] 1 sample 4 to12 h post-dose[b,c]
	24 and 48	1 sample pre-dose[a]
EFV PK	8, 24, 36, and 48	1 sample mid-dosing interval[d]

DTG = dolutegravir; EFV = efavirenz; h = hour; PK = pharmacokinetic

a. Pre-dose samples to be collected immediately before the morning dose (i.e. within 15 minutes) which will be taken under observation at the clinic. DTG twice-daily pre-dose sample be drawn as close as possible to 12 hours after the previous dose and DTG once-daily pre-dose sample should be drawn as close as possible to 24 hours after the previous dose.
b. Both sample time points must be obtained **from each subject**.
c. It is acceptable to draw the 4 to 12 hour sample any time between 4 and 12 hours post-dose.
d. Mid-dosing interval samples should be collected in the morning at about 12 hours after the evening EFV dose on previous day.

The Week 8 PK visit is to collect PK data during the TB treatment. If the subject is not on TB treatment at Week 8 due to temporary interruption for the management of toxicity, then PK data should instead be collected 14 to 21 days after RIF reintroduction. The Week 36 PK visit is to collect PK data when the subject has completed TB treatment (i.e., the subject is no longer taking RIF). If the treatment course has been extended because of interruptions, collection of Week 36 data should be delayed until TB treatment completion. The Week 24 and 48 PK data will correspond with the primary and secondary efficacy analysis, respectively. Collection of PK data at multiple visits will provide more robust analysis of inter-occasional variability as well as possible evaluation of dosing compliance.

It is important to collect PK samples according to the following specified procedure.

For subjects randomly assigned to the DTG arm

DTG twice daily - While taking **DTG twice daily** following TB treatment completion it is critical that the pre-dose sample should be drawn as close as possible to 12 hours after the previous dose (target window = 10 to 14 hours after the last dose) and before that morning's dose (i.e., within 15 minutes of the next dose). For the 3 days in advance of a PK clinic visit, the subject must be instructed to plan the dosing of DTG at a time that corresponds with the scheduled PK visit time to allow for a pre-dose sample collection as close to 12 hours after the previous dose.

DTG once daily - While taking **DTG once daily** following TB treatment completion it is critical that the pre-dose sample should be drawn as close as possible to 24 hours after the previous dose (target window = 22 to 26 hours after the last dose) and before that morning's dose (i.e., within 15 minutes of the next dose). For the 3 days in advance of a PK clinic visit, the subject must be instructed to plan the dosing of DTG at a time that corresponds with the scheduled PK visit time to allow for a pre-dose sample collection as close to 24 hours after the previous dose.

After the pre-dose sample is taken, the next dose will be taken under observation at the clinic.

To enhance the quality of PK data collection, subjects will be asked to complete a diary card with the date and time of IP administration prior to the scheduled PK clinic visits. The actual dates and times of DTG dosing during the 3 days of prior to PK sampling as well as the observed dose taken at the clinic, if the subject vomited, and the actual date and time of the PK samples must be recorded on the eCRF.

Note: If a subject presents at the clinic for pre-dose PK sample collection having already taken the morning dose or having missed doses within the previous 3 days, it is recommended to reschedule PK sampling at the earliest next clinic visit. It is not recommended to collect PK samples if date and time of dosing for the previous 3 days cannot be reliably confirmed. Such samples will be discarded and will not contribute to any analyses.

Flexibility is allowed in collecting the post-dose sample (anywhere from 1 to 3 hours and 4 to 12 hours post-dose) so that a range of sample times can be obtained. To achieve this, subjects may choose to remain in clinic until at least 1 hour after taking the DTG dose and may choose to return to the clinic 4 to 12 hours after taking the medication.

For subjects randomly assigned to the EFV arm

For subjects on EFV, the mid-dose samples will be collected in the morning, approximately 12 hours after the previous day's dose. The date and time of the EFV mid-dose sample, as well as the date and time the subject had taken the previous 3 doses of EFV, will be collected and recorded on the CRF.

6.5.3. Bioanalysis of DTG and EFV PK Samples

Plasma will be extracted from the blood samples collected and shipped for determination of DTG and EFV plasma concentrations by validated LC/MS/MS assays under the control of GSK PTS DMPK/Scinovo, the details of which will be included in the SPM. Raw data will be archived at the bioanalytical site (detailed in the SPM).

Once the plasma has been analyzed for DTG and EFV, any plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS DMPK protocol.

6.6. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject at Screening for resistance testing at the central laboratory (or a laboratory contracted by the central laboratory) and on study 'plasma for storage samples' according to the Time and Events schedule in Section 6.1 for potential viral genotypic and phenotypic analyses. In addition, whole venous blood samples will be obtained from each subject to provide plasma for storage samples at the time of re-test for suspected protocol-defined virologic failure as specified in the Quest Laboratory manual.

Details concerning the handling, labeling and shipping of these samples will be supplied separately. Viral genotype will be performed at Screening for study eligibility determination through Quest Diagnostics as well as at location(s) to be described in the SPM. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard Phenosense and GenoSure testing methods for protease (PRO), reverse transcriptase (RT), and integrase assays. In addition, where Monogram Biosciences resistance testing is not possible, resistance testing may also be performed at location(s) to be described in the SPM.

6.6.1. Viral Endpoint

A secondary endpoint of this study will be the incidence of treatment-emergent genotypic and phenotypic resistance to DTG, EFV, and other on-study ART in subjects meeting confirmed virologic withdrawal criteria.

6.6.2. HIV-1 Polymerase Viral Genotyping and Phenotyping

Subjects meeting 'confirmed virologic withdrawal criterion' will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from samples collected at the time of meeting 'suspected virologic withdrawal criterion' (additional subsequent samples may be analyzed); these results will be reported to the investigator as soon as available to provide guidance for election of an alternate regimen.

HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the Baseline isolates from all subjects, if possible. When samples cannot be analyzed by Monogram Biosciences, Baseline isolate resistance testing may be performed at location(s) to be described in the SPM.

6.6.3. HIV-1 Exploratory Analysis

Additional analyses for HIV-1 resistance may, for example, be carried on stored plasma samples from Baseline and other relevant time points. These analyses may include but are not limited to additional viral genotyping and/or phenotyping, as well as other virologic evaluations such as linkage and minority species analyses, low level HIV-1 RNA quantitation, and measurement of viral replicative capacity. HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the Baseline and the last on-treatment isolates from subjects who have HIV-1 RNA >400 c/mL regardless of confirmatory HIV-1 RNA.

6.7. Pharmacogenetic Research

Information regarding pharmacogenetic (PGx) research is included in Section 11.1.

The IEC/IRB and, where required, the applicable regulatory agency, must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (see Section 11.1). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and, therefore, PGx assessments will not be conducted.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK-defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug. Electronic CRFs (including queries and audit trails) will be sent at the end of the study in CD format to GSK to be retained. Each investigator will receive a copy of his or her site-specific data in the same format to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to ViiV/GSK according to ViiV/GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

This study is designed to assess the antiviral effect of treatment with a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily) at Week 48, when administered in combination with dual NRTI therapy. No formal statistical hypothesis testing will be performed.

8.1.1. Sample Size Assumptions

Data from recent DTG studies in treatment-naïve subjects have shown consistent response rates of 88% to 90% at Week 48 with a dose of 50 mg once daily (Table 9). Primary analyses in these studies have shown non-inferiority to RAL 400 mg once daily and superiority to both EFV/TDF/FTC once daily and DRV/r once daily. The proportion of subjects with baseline HIV-1 RNA >100,000 c/mL in the Phase III studies ranged from 25% to 32%; there were few subjects with baseline CD4+ cell counts <50 cells/mm^3.

Table 9 Week 48 Results From Recent Treatment-Naïve DTG Studies

Study	Back-ground NRTI	Endpoint	Active Treatment Response[a]	Comparator/ Control Response	Notes
SINGLE Phase III n=833		HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg +ABC/3TC once daily 88% (87%)[a]	EFV/TDF/FTC once daily 81% (80%)[a]	DTG superior (at Wk 48/96) Baseline: 32% >100,000 c/mL HIV-1 RNA
SPRING-2 Phase III n=822	ABC/3TC or TDF/FTC	HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg once daily 88% (87%)[a]	RAL 400 mg BID 85% (86%)[a]	DTG non-inferior (at Wk 48/96) Baseline: 28% >100,000 c/mL HIV-1 RNA
FLAMINGO Phase IIIb n=484	ABC/3TC or TDF/FTC	HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg once daily 90% (88%)[a]	DRV/r 800 mg/100 mg once daily 83% (80%)[a]	DTG superior at Wk 48 (study continuing to Wk 96) Baseline: 25% >100,000 c/mL HIV-1 RNA
SPRING-1 Phase IIb n=205	ABC/3TC or TDF/FTC	HIV-1 RNA <50 c/mL; TLOVR	DTG 50 mg once daily 90%	EFV 600 mg once daily 82%	DTG 10 mg 91% DTG 25 mg 88% Baseline: 21% >100,000 c/mL HIV-1 RNA

ABC/3TC = abacavir/lamivudine; c = copies; CD4 = helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4); DRV/r = darunavir + ritonavir; DTG = dolutegravir; EFV = efavirenz; EFV/TDF/FTC = efavirenz/tenofovir disoproxil fumarate/emtricitabine; FDA = Food and Drug Administration (United States); HIV = human immunodeficiency virus; mL = milliliter; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RNA = ribonucleic acid; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; TLOVR = time to loss of virologic response; Wk = week.

a. Response rate for subjects with baseline CD4+ cell count ≥50 to <500 cells/mm^3, where available.

Response rates <50 c/mL in the REFLATE study at Week 48 were much lower than seen in the DTG studies (Table 10). The study population included higher proportions of subjects with baseline HIV-1 RNA >100,000 c/mL (46%) and with baseline CD4+ cell counts <50 cells/mm^3 (20%); in particular, the EFV treatment arm had more such subjects than either of the RAL treatment arms. These characteristics are typically associated with a lower response rate for achieving virologic suppression.

Table 10 Week 48 Results from the REFLATE Study

Back-ground NRTI	Endpoint	EFV Once Daily (Response Rate)	RAL Twice-Daily (Response Rate)	Notes
TDF/FTC	<50 c/mL; Missing=Failure	600 mg (67%)	400 mg (76%) 800 mg (63%)	n=51 in each arm Baseline: CD4+ cells <50 c/mL: 27%, 24%, and 10%[a] HIV-1 RNA >100,000 c/mL: 51%, 39%, 47%[a]

c = copies; EFV = efavirenz; HIV = human immunodeficiency virus; mL = milliliter; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RNA = ribonucleic acid; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

a. Percentage of subjects at Baseline in EFV 600 mg, RAL 400 mg, and RAL 800 mg treatment groups, respectively

Rates of withdrawal due to non-fatal AEs were comparable between REFLATE and the DTG studies. There was a higher incidence of deaths in REFLATE (approximately 5% overall versus <1% in DTG studies) with many owing to complications with TB co-infection. Even accounting for differences in the study population, the REFLATE response rates are lower than would be expected based on results seen in the DTG studies. The smaller sample sizes in REFLATE are more sensitive to what may be other chance findings.

Given the exposure data, it is anticipated that DTG twice daily co-administered with RIF will have efficacy comparable to DTG once daily, but a study population with higher proportions of subjects with baseline HIV-1 RNA >100,000 c/mL and lower CD4+ cell counts would have slightly lower responses than seen in the prior DTG studies.

Assuming an 85% response rate for DTG at Week 48, a sample size of 66 to 72 subjects in the DTG arm would have >85% power to detect a response rate of greater than 70% (Figure 4). Although the objective of the study is not to test a statistical hypothesis, the sample size has been chosen to provide an adequate number of subjects for assessing the antiretroviral activity of DTG.

8.2. Study Design Considerations

8.2.1. Sample Size Sensitivity

Figure 4 shows the relationship between study power and sample size, assuming an 85% response rate for DTG, to detect a response rate of greater than 70%. A sample size of 69 subjects has >90% power. Smaller samples (e.g., 65 or greater) have at least 86% power, which is relevant when assessing the primary endpoint in alternate analysis populations (i.e., modified ITT-E).

Figure 4 Relationship Between Study Power and Sample Size

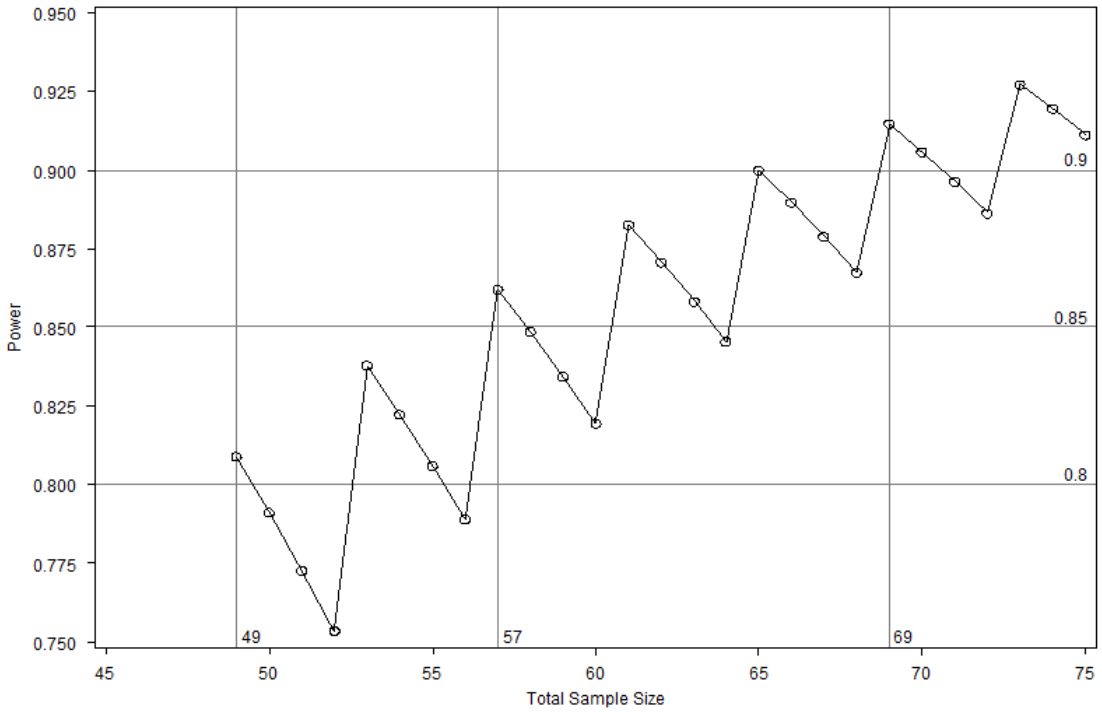
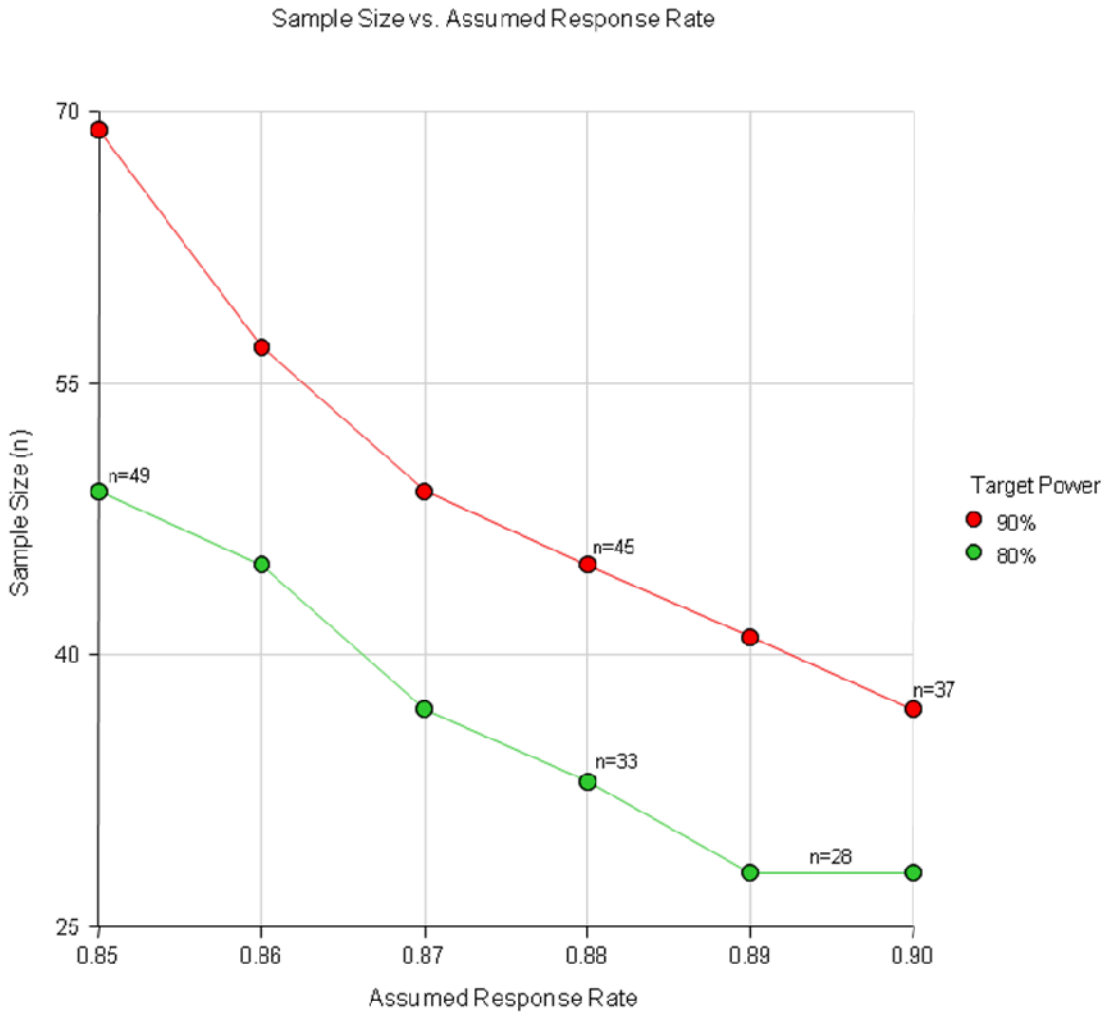


Figure 5 shows the relationship between minimum sample size required and the assumed response rate; different targets for power are considered.

Figure 5 Relationship Between Minimum Sample Size Required and the Assumed Response Rate



8.2.2. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

8.2.3. Analysis Populations

The following populations will be assessed; other analysis populations (e.g., per-protocol, genotypic/phenotypic) will be fully described in the RAP.

8.2.3.1. Intent-to-Treat Exposed (ITT-E) Population

The intent-to-treat exposed (ITT-E) population will consist of all randomly assigned subjects who receive at least one dose of IP. Subjects will be assessed according to their randomized treatment, regardless of the treatment they received. Unless stated otherwise, the ITT-E population will be used for summaries of efficacy.

8.2.3.2. Modified Intent-to-Treat Exposed (MITT-E) Population

The modified intent-to-treat exposed (MITT-E) population will consist of all subjects in ITT-E population with confirmed RIF-sensitive MTB. This population will be used in an additional evaluation of the primary endpoint.

8.2.3.3. Per-Protocol Population

The per-protocol (PP) population will consist of subjects in the ITT-E population with the exception of major protocol violators, e.g. violations which could affect the assessment of antiviral activity. The PP population will be used for sensitivity analyses of the primary efficacy endpoint.

8.2.3.4. Safety Population

The safety population is defined as all subjects who receive at least one dose of IP. Subjects will be analyzed according to the actual treatments received.

8.2.3.5. PK Population

8.2.3.5.1. DTG PK Population

All subjects enrolled in the study who received at least 1 dose and for whom any pre-dose, post-dose, or mid-dose sample was taken for PK analysis with evaluable drug concentration data reported.

8.2.3.5.2. EFV PK Population

All subjects enrolled in the study who received at least 1 dose and for whom any mid-dose sample was taken for PK analysis with evaluable drug concentration data reported.

8.2.4. Analysis Data Sets

Final analysis will be performed after the completion of the study and authorization of final dataset.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by subject, study period or phase, day, and time, noting treatment arm; summaries will be presented by treatment arm, day, and time.

For the primary efficacy analysis, each subject's response (i.e., HIV-1 RNA <50 c/mL) will be calculated according to the US Food and Drug Administration (FDA)'s Snapshot algorithm. This algorithm treats all subjects without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of IP prior to visit window) as non-responders, as well as subjects with ART substitutions not permitted per protocol (see Section 5.1.5).

Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the subject is on-treatment within the visit window of interest (to be specified in the RAP). Full details on this Snapshot algorithm will be contained in the RAP.

For this study, all protocol-permitted substitutions, regardless of HIV-1 RNA results at the time of the substitution, will have no effect on the analysis.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.1 or higher of the SAS system will be used to analyze the data and to generate tables, figures, and listings.

Complete details will be documented in the RAP.

8.2.5. Treatment Comparisons

No formal treatment comparisons will be performed in this study.

8.2.6. Interim Analysis

The first interim analysis will be conducted when all subjects complete their Week 24 visit. The primary analysis will be conducted when all subjects complete their Week 52 visit. A final end-of-study analysis will be conducted when the final subject randomly assigned to the DTG OLE has transitioned to commercial supplies of DTG or has been withdrawn from the study. Further data cuts and analyses may be conducted as necessary in order to support regulatory submissions and publications.

8.2.7. Key Elements of Analysis Plan

When descriptive statistics are used to summarize group characteristics or differences, the following statistics will be included: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

8.2.7.1. Efficacy Analyses

The primary efficacy endpoint, the proportion of subjects from the ITT-E population with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the DTG arm, will be presented with its 95% CI.

The following secondary efficacy endpoints will be summarized using descriptive statistics:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the EFV arm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related AE, safety stopping criteria, or lack of efficacy);
- Changes from baseline in CD4+ counts at Week 24 and Week 48.

The following tertiary efficacy endpoint will be summarized by event type and treatment arm using descriptive statistics:

- Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses, and death);
- Proportion of subjects with TB treatment success (using the WHO definition);
- Proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment.

8.2.7.2. Safety Analyses

Exposure to IP, measured by the number of weeks on IP, will be summarized by treatment arm. The proportion of subjects reporting AEs will be tabulated by treatment arm. The following summaries of AEs will be provided:

- Incidence and severity of all AEs, SAEs, and laboratory abnormalities;
- Proportion of subjects who permanently discontinue IP due to AEs or death;
- Proportion of subjects who temporarily discontinue IP and/or TB therapy due to AEs;
- Proportion of subjects with TB-associated IRIS.

In addition, absolute values and changes over time in laboratory parameters will be analyzed. Laboratory data will be summarized by visit and treatment arm. The number and percentage of subjects with graded laboratory toxicities (based on DAIDS categories, see Section 11.3) will be summarized by treatment arm.

Further details of safety analyses will be included in the RAP.

8.2.7.3. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

Concentrations of DTG and EFV at Weeks 8, 24, 36, and 48 upon initiation of DTG or EFV therapy will be analyzed using population PK modeling approach to estimate AUC, Cmax, and $C\tau$ for individual subjects at Week 48 final analysis. The population PK analysis result will be presented in a separate PK report.

Week 24 interim analyses and Week 48 final analyses of DTG and EFV concentrations based on sparse PK sampling will be summarized using descriptive statistics.

The relationship between DTG/EFV IP exposure and the Week 24 and Week 48 anti-HIV responses (Snapshot) may be evaluated using univariate (and multivariate) logistic regression analysis as well as graphic exploration.

Detailed analysis will be provided in the RAP.

8.2.7.4. Viral Genotyping/Phenotyping Analyses

The incidence of treatment-emergent genotypic and phenotypic resistance to DTG, EFV, and other on-study ART in subjects meeting confirmed virologic withdrawal criteria will be summarized using descriptive statistics.

8.2.7.5. Pharmacogenetic Analyses

See Section 11.1 for details about the pharmacogenetics analysis plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, ViiV/GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH E6(R1) GCP guidelines and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

ViiV/GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described Section 11.1, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and PPD procedures, PPD monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ViiV, GSK, or PPD requirements. When reviewing data collection procedures, the discussion will include identification, agreement, and documentation of data items for which the eCRF will serve as the source document.

PPD will monitor the study to ensure the following:

- Data are authentic, accurate, and complete;
- Safety and rights of subjects are being protected;
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, ViiV/GSK/PPD may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit, or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

Unless terminated early, this study will be considered completed after the last subject transitions to commercial supplies of DTG. Upon completion or termination of the study, the PPD monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and PPD SOPs.

ViiV/GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If ViiV/GSK determines that such action is required, ViiV/GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, ViiV/GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, ViiV/GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. ViiV/GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a ViiV/GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

ViiV, GSK, or PPD will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, ViiV/GSK standard operating procedures, and/or institutional requirements.

The investigator must notify ViiV, GSK, or PPD of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, and Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ViiV/GSK site or other mutually-agreeable location.

ViiV/GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

10. REFERENCES

Babu Swai O, Aluoch JA, Githui WA et al. Controlled clinical trial of a regimen of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. Tubercle. 1988;69(1):5-14.

Bertrand J, Verstuyft C, Chou M et al. CAMELIA (ANRS 1295-CIPRA KH001) Study Group. Dependence of efavirenz- and rifampicin-isoniazid-based antituberculosis treatment drug-drug interaction on CYP2B6 and NAT2 genetic polymorphisms: ANRS 12154 study in Cambodia. J Infect Dis. 2014;209(3):399-408.

Boulle A, Van Cutsem G, Cohen K et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. JAMA. 2008;300(5):530-539

British Thoracic Association (BTA). A controlled trial of six months chemotherapy in pulmonary tuberculosis. Second report: results during the 24 months after the end of chemotherapy. Am Rev Respir Dis. 1982;126(3):460-2.

British Thoracic Society (BTS). A controlled trial of 6 months' chemotherapy in pulmonary tuberculosis. Final report: results during the 36 months after the end of chemotherapy and beyond. Br J Dis Chest. 1984;78(4):330-6.

Cahn P, Pozniak AL, Mingrone H et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382(9893):700-8.

Castagna A, Maggiolo F, Penco G et al. for the VIKING-3 Study Group. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. J Infect Dis. 2014;1-9. [Epup ahead of print]

Centers for Disease Control and Prevention (CDC). Managing drug interactions in the treatment of HIV-related tuberculosis 2013. Available at http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/pdf/tbhiv.pdf. Accessed on 10 April 2014.

Centers for Disease Control and Prevention (CDC). Treatment of Tuberculosis;American Thoracic Society, CDC, and Infectious Diseases Society of America (2003). Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm. Accessed 27 March 2014.

Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax 1998;53(7):536–48.

Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability. The report of final results. Ann Intern Med. 1990; 112(6):397-406.

Department of Health and Human Services (DHHS), Food and Drug Administration and Center for Drug Evaluation and Research. DRAFT Guidance for industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. June 2013. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf. Accessed on 16 October 2013.

Department of Health and Human Services (DHHS), Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed on 28 March 2014 [p.192, K-12 Table 13]

Department of Health and Human Services (DHHS). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-1-infected adults and adolescents: recommendations from the CDC, the NIH, and the HIV Medicine Association of the Infectious Diseases Society of America. June 2013. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed on 27 March 2014 [p.67 and 68; Figure 8 and Figure 9]

Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampicin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013;62(1):21-7.

ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet. 2014; [Epub ahead of print]

Eron JJ, Clotet B, Durant J, et al. for the VIKING Study Group. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis. 2013;207(5):740-8.

European AIDS Clinical Society (EACS) Guidelines for the treatment of HIV infected adults in Europe. Version 7.0. 2013. Available at http://www.eacsociety.org/Guidelines.aspx. Accessed on 09 April 2014

Getahun H, Gunneberg C, Granich R, et al. HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis. 2010;50 Suppl 3:S201-7.

GlaxoSmithKline (GSK) Document Number RM2007/00683/11: Clinical Investigator's Brochure for GSK1349572 (Dolutegravir) Version 11. October 2017.

GlaxoSmithKline Document Number 2013N177327_00: ING112574 Clinical Study Report. A Phase III Study to Demonstrate the Antiviral Activity and Safety of Dolutegravirin HIV-1 Infected Adult Subjects with Treatment Failure on an Integrase Inhibitor Containing Regimen (ING112574 –Week48Results of All Subjects Enrolled [N=183]) December 2013.

GlaxoSmithKline (GSK) Document Number RM2007/00683/11: Clinical Investigator's Brochure for GSK1349572 (Dolutegravir) Version 11. October 2017.

GlaxoSmithKline Document Number 2017N352880_00: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 01, 11 December 2017.

GlaxoSmithKline Document Number 2017N352880_01: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 02, June 2018.

Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. Lancet Infect Dis. 2014 Apr 9. pii: S1473-3099(14)70711-X. doi: 10.1016/S1473-3099(14)70711-X.

Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011;365(16):1482-91.

Inker LA, Schmid CH, Tighiouart H et al. CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20-9.

International AIDS Society (IAS)-USA. Update of the Drug Resistant Mutations in HIV-1: March 2013. Topics in HIV Medicine 2013;21(1): 6-14.

Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampicin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. Clin Infect Dis. 2013;57(4):586-93.

Meintjes G, Lawn SD, Scano F, et al. International Network for the Study of HIV-associated IRIS. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008;8(8):516-23.

Oquendo MA, Halberstam B, Mann JJ. Risk Factors for suicidal behavior: the utility and limitations of research instruments (2003). In M.B. First [Ed] Standardized Evaluation in Clinical Practice, pp 103-30.

Oxford Textbook of Palliative Medicine, Oxford University Press. Edited by Geoffrey Hanks and Nathan I. Cherny. 1993;109.

Pozniak AL, Coyne KM, Miller RF et al. British HIV Association (BHIVA) guidelines for the treatment of TB/HIV coinfection 2011. HIV Med. 2011;12(9):517-24.

Raffi F, Jaeger H, Quiros-Roldan E et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naïve adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013a;13(11):927-35.

Raffi F, Rachlis A, Stellbrink HJ et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013b;381(9868):735-43.

Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee. Am J Respir Crit Care Med 2006; 174(8): 935–52.

Sirturo (bedaquiline) Product Information, November 2013.

Slutkin G, Schecter GF, Hopewell PC. The results of 9-month isoniazid-rifampin therapy for pulmonary tuberculosis under program conditions in San Francisco. Am Rev Respir Dis. 1988;138(6):1622-4.

Sustiva (efavirenz) EU Product Information, Jan 2014: Viewed on 28 March 2014 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000249/human_med_001068.jsp&mid=WC0b01ac058001d124

Sustiva (efavirenz) US Product Information, May 2013, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020972s043,021360s031lbl.pdf

Tivicay (dolutegravir) EU Summary of Product Characteristics (SmPC). Available at: http://www.viivhealthcare.com/our-medicines/tivicay.aspx. Accessed on 28 March 2014

Tivicay (dolutegravir) US Prescribing Information, August 2013. Available at http://www.viivhealthcare.com/our-medicines/tivicay.aspx. Accessed on 28 March 2014

Török ME and Farrar J. When to start antiretroviral therapy in HIV-associated tuberculosis. N Engl J of Med 2011;365(16):1538-40.

Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369(19):1807-18.

World Health Organization (WHO). Global Tuberculosis Report 2013. Available at: http://www.who.int/tb/publications/global_report/en/. Accessed on 28 Mar 2014

World Health Organization (WHO). Treatment of Tuberculosis: Guidelines – Fourth Edition 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf. Accessed on 28 Mar 2014

11. APPENDICES

11.1. Appendix 1 Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	*HLA-B* 57:01 (Human Leukocyte Antigen B)*	Carriage of the *HLA-B*57:01* variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective *HLA-B*57:01* screening and exclusion of *HLA-B*57:01* positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective *HLA-B*57:01* screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. *HLA-B*57:01* screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.

Drug	Disease	Gene Variant	Outcome
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	*HLA-B*15:02*	Independent studies indicated that patients of East Asian ancestry who carry *HLA-B*15:02* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of *HLA-B*15:02* prior to initiating treatment with carbamazepine.
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	*UGT1A1*28*	Variations in the *UGT1A1* gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular *UGT1A1* gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have 2 copies of the *UGT1A1*28* variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to DTG.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to DTG. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with DTG, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Efficacy
- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety (tolerability and IRIS monitoring)

Study Population

Any subject who is enrolled in the clinical study can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for DNA extraction and used in PGx assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (approximately 6 mL) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of DTG has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to DTG.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (absorption, distribution, metabolism and excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to DTG. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results

of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarise the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

References

Chung WH, Hung SI, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin. Drug Saf. 2010;9:15-21.

Ferrell PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008;9:1543-6.

Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359:1121-2.

Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol. 2004;22:1382-8.

Liu CY, Chen PM, Chiou TJ, et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer. 2008;112:1932-40.

Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002;359:727-32.

Mallal S, Phillips E, Carosi G, et al. PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358:568-79.

Schulz C, Heinemann V, Schalhorn A, et al. UGT1A1 gene polymorphism: Impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. World J. Gastroenterol. 2009;15:5058-66.

11.2. Appendix 2 CDC Classification System for HIV-1 Infections (1993)

Clinical Categories

The clinical categories of HIV infection are defined as follows:

Category A

Category A consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B (Symptomatic non-AIDS conditions)

Category B consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. **Examples** of conditions in clinical Category B include, **but are not limited to**:

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least 2 distinct episodes or more than 1 dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

For classification purposes, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal

candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in clinical Category B.

Category C (AIDS indicator conditions as defined by diagnostic or presumptive measures).

Category C includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

Conditions in Category C include:

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration);or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent

- Toxoplasmosis of brain
- Wasting syndrome due to HIV
- Non-CDC, HIV-associated conditions.

Reference:

Castro GK, Ward JW, Slutsker L, et al. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992;41(No. RR-17):1-19.

11.3. Appendix 3 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for adverse event (AE) reporting. A grading (severity) scale is provided for each AE term.

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia,	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
and Myalgia				
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult >15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm2 –	Erythema OR Induration OR Edema > 9 cm any diameter (or	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess	Necrosis (involving dermis and deeper tissue)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
		81cm2)	> 81 cm2)	OR Drainage	
	Pediatric ≤15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)		Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL					
Alopecia		Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash		Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation		Slight or localized	Marked or generalized	NA	NA

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hypopigmentation		Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)		Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR					
Cardiac arrhythmia (general) (By ECG or physical exam)		Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction		NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)		NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children >10 cc/kg) indicated
Hypertension					
	Adult >17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
	Pediatric ≤17 Years (with repeat testing at same	NA	91st – 94th percentile adjusted for age, height, and gender	95th percentile adjusted for age, height, and gender (systolic and/or	Life-threatening consequences (e.g., malignant hypertension) OR

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	visit)		(systolic and/or diastolic)	diastolic)	Hospitalization indicated (other than emergency room visit)
Hypotension		NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion		Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval					
	Adult >16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
	Pediatric ≤16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc					
	Adult >16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
	Pediatric ≤16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diarrhea					
	Adult and Pediatric ≥1 year	Transient or intermittent episodes of unformed stools OR Increase of 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
	Pediatric <1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia		Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis		Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea		Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis		NA	Symptomatic AND Hospitalization not indicated (other than emergency room	Symptomatic AND Hospitalization indicated (other than emergency	Life-threatening consequences (e.g., circulatory failure, hemorrhage,

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
		visit)	room visit)	sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – Pediatric ≤16 Years	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) – Adult ≥18 years See also Seizure: (known pre- existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) – Adult ≥ 18 years For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Seizure – Pediatric <18 years		Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post-ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with <24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without Secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)		NA	Present	NA	NA
Vertigo		Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care Functions
RESPIRATORY					
Bronchospasm (acute)		FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress					
	Adult ≥14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support Indicated
	Pediatric <14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
MUSCULOSKELETAL					
Arthralgia See also Arthritis		Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care Functions
Arthritis See also Arthralgia		Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss					
	Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
	Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
Myalgia (non-injection site)		Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis		NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, Mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
infection)				
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
		control	modification	
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY ***Standard International Units are listed in italics***				
Absolute CD4+ count **– Adult and Pediatric >13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/ mm^3 *200 – 299/µL*	100 – 199/ mm^3 *100 – 199/µL*	< 100/ mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric >13 years** (HIV NEGATIVE ONLY)	600 – 650/ mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/ mm^3 *0.500 x 109 – 0.599 x 10^9/L*	350 – 499/ mm^3 *0.350 x 109 – 0.499 x 10^9/L*	< 350/ mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, >7 days	1,000 – 1,300/ mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/ mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/ mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/ mm^3 *< 0.500 x 10^9/L*
Infant†, 2 – ≤ 7 days	1,250 – 1,500/ mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/ mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/ mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/ mm^3 *< 0.750 x 10^9/L*
Infant†, ≤ 1 day	4,000 – 5,000/ mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/ mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/ mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/ mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Adult and Pediatric ≥57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62 – 5.23 mmol/L*	6.50 – 7.4 g/dL *4.03 – 4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult and Pediatric ≥57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *2.14 – 2.78 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Infant†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 – 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant†, ≤21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59 – 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
International Normalized Ratio of prothrombin time	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
(INR)				
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES *Standard International Units are listed in italics*				
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alkalosis		NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)		1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)		1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low		16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)					
	Adult and Pediatric >14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
	Infant†, ≤14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
	Infant†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)					
	Adult and Pediatric ≥7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
	Infant†, <7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)					
	Adult and Pediatric ≥7 days	7.8 – 8.4 mg/dL	7.0 – 7.7 mg/dL	6.1 – 6.9 mg/dL	< 6.1 mg/dL

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	1.95 – 2.10 mmol/L	*1.75 – 1.94 mmol/L*	*1.53 – 1.74 mmol/L*	*< 1.53 mmol/L*
Infant†, <7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric <18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high					
	Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
	Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low					
	Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
	Infant†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate		ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
LDL cholesterol (fasting)					
	Adult ≥18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
	Pediatric >2 – <18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric >14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric <1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L	125 – 129 mEq/L	121 – 124 mEq/L	≤ 120 mEq/L

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	130 – 135 mmol/L	*125 – 129 mmol/L*	*121 – 124 mmol/L*	*≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS *Standard International Units are listed in italics*				
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random Collection	1 +	2 – 3 +	4 +	NA
		LABORATORY		
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria, 24 hour collection				
Adult and Pediatric ≥10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *>3.500 g/d*
Pediatric > 3 mo -<10 years	201 – 499 mg/m^2/24 h	500 – 799 mg/m^2/24 h	800 – 1,000 mg/m^2/24 h	> 1,000 mg/ m^2/24 h

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	0.201 – 0.499 g/d	*0.500 – 0.799 g/d*	*0.800 – 1.000 g/d*	*> 1.000 g/d*

11.4. Appendix 4 Country-Specific Requirements

No country-specific requirements exist.

11.5. Appendix 5 Liver Safety Drug Restart or Rechallenge Guidelines

GUIDELINES FOR DRUG RESTART OR RECHALLENGE AFTER STOP FOR LIVER CRITERIA

1. **IP rechallenge** may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if favorable benefit: risk and no alternate medicine available. (Figure 6 and Table 11).
2. **IP restart** may be considered for liver safety events with a clear underlying cause (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis, or hypersensitivity [fever, rash or eosinophilia] and drug not associated with HLA genetic marker of liver injury, when liver chemistries have improved to normal or are within 1.5 × baseline and ALT<2 × ULN).
3. Subjects meeting liver chemistry stopping criteria that present rebound of ALT elevation upon stepwise re-exposure to TB treatment regimen (see Section 6.4.3.1 for suggestion on TB treatment re-introduction regimens) will be considered as having the anti-TB treatment as the likely cause of ALT elevation. If the TB treatment component considered to be the likely cause of the ALT elevation is not RIF and an alternative anti-TB treatment containing RIF can be successfully introduced, the authorization for restarting the IP may be discussed between the investigator and the study medical monitor without the need for approval from the VSLC. If there is no evidence of a relationship between one of the antituberculosis anti-TB treatment regimen components (other than RIF) and the ALT elevation, the case will need VSLC approval to restart DTG (this approval can be ad hoc).

Background: Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies**. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered in 1 month of initial injury [Andrade, 2009]. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- Jaundice or bilirubin ≥2 × ULN with initial liver injury
- Prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- Evidence of drug-related preclinical liability (e.g., reactive metabolites; mitochondrial impairment [Hunt, 2010])

Decision Process for Drug Rechallenge Approval or Disapproval

- Principal investigator (PI) requests consideration of drug rechallenge for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternate treatment.

- Medical monitor and Global Clinical Safety and Pharmacovigilance (GCSP) physician to review the subject's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and complete checklist (Table 11).

- The medical monitor and GCSP physician are accountable to review and agree on the following:

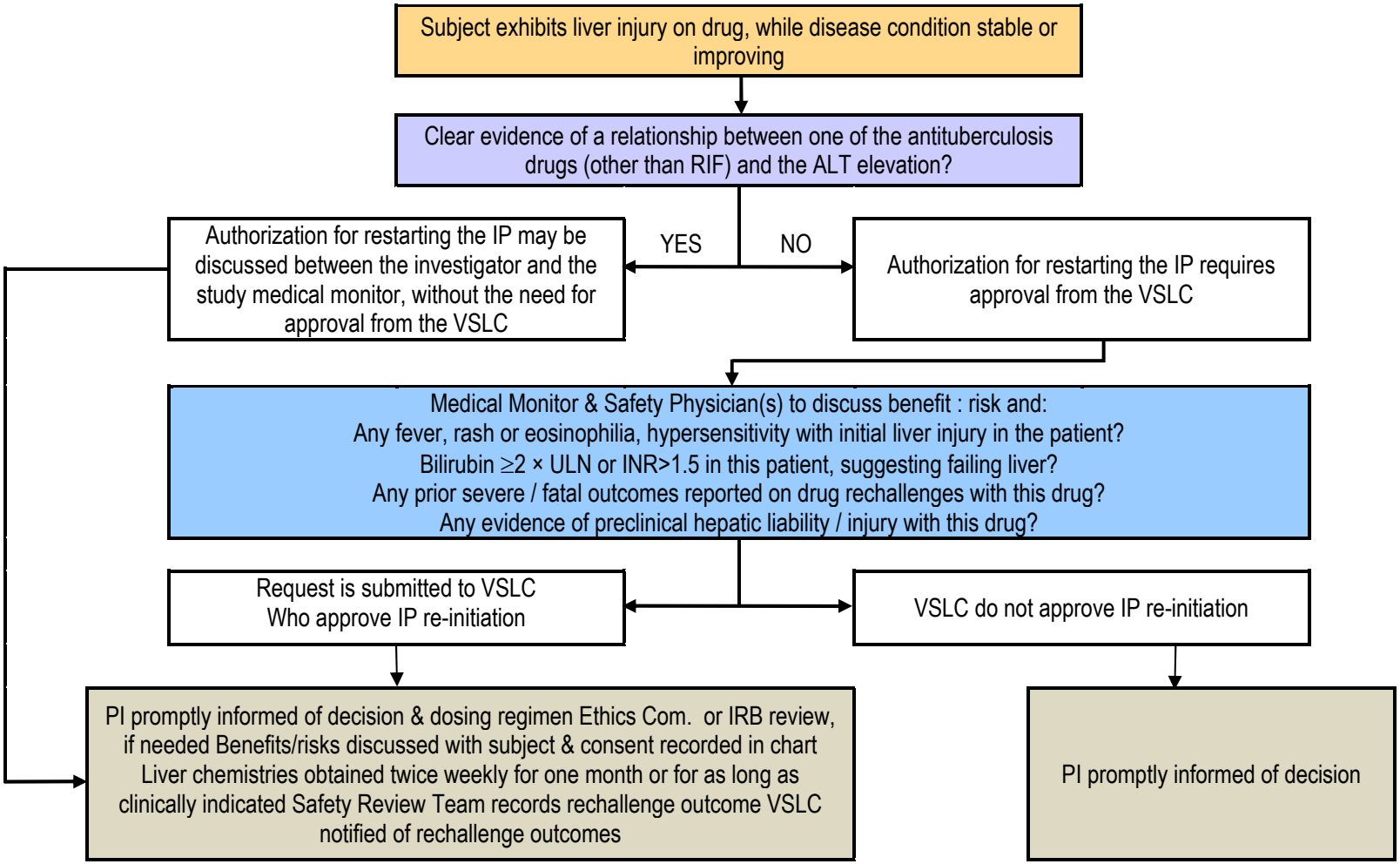
  1. Compelling benefit of the IP for this subject and no alternate therapy
  2. Relative benefit-risk of drug rechallenge, with consideration of the following high risk factors:

     - Initial liver injury event included: fever, rash, eosinophilia, or bilirubin >2 × ULN (or direct bilirubin >35% of total, if available)
     - Subject currently exhibits severe liver injury defined by: ALT >3 × ULN, bilirubin >2 × ULN (direct bilirubin >35% of total, if available), or INR>1.5
     - SAE or fatality has earlier been observed with IP rechallenge
     - IP associated with known preclinical hepatic liability/injury

- Relevant physicians must review and agree on request for drug rechallenge:

  - Safety Team Leader, study medical monitor and Physician Product Leader Medicines Development Leader, and Project Physician Leader (GSK).
  - Medicines Development Leader and Project Physician Leader (GSK).
  - Request is taken to full VSLC for final decision

Figure 6 VSLC Process for Drug Rechallenge Approval or Disapproval



The local operating company (LOC) medical director (ViiV and GSK where applicable) should be informed that IP rechallenge is under consideration and of the final decision, whether or not to proceed.

Table 11 Checklist for IP Rechallenge for Critical Medicine (Following Drug-Induced Liver Injury, IP Rechallenge is Associated with 13% Mortality Across all Drugs in Prospective Studies)

	Yes	No
Relative benefit-risk favorable for drug rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
○ fever, rash, eosinophilia, or hypersensitivity		
○ or bilirubin ≥ 2 × ULN (direct bilirubin >35% of total)		
○ Subject currently exhibits ALT ≥ 3xULN, bilirubin ≥ 2 × ULN (direct bilirubin >35% of total, if available), or INR ≥ 1.5		
○ SAE or fatality has earlier been observed with IP rechallenge **If yes, please provide brief explanation**:		
○ IP associated with known preclinical hepatic liability/injury		
○ Source data defining the subjects current resistance profile		
○ Previous drug history		

Medical monitor, GCSP Physician, and PI actions for Restart or Rechallenge following VSLC decision

Medical Monitor and (Global Clinical Safety and Pharmacovigilance) GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's rechallenge (or restart) decision and recommended dosing regimen in writing and medical monitor must record note in study files.
- The Safety Review Team must record rechallenge (or restart) outcomes and the GCSP Physician must send these to the VSLC
- All severe reactions (rechallenge associated with bilirubin >2 × ULN or jaundice, or INR ≥1.5), SAEs, or fatalities with drug rechallenge (or restart) must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy, and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions

- The PI must obtain IRB or IEC approval of IP rechallenge or restart, as required.
- If IP re-initiation is approved, the subject must provide informed consent with a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.

Targeted IP rechallenge or IP restart informed consent form must be used.

- The subject's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by medical monitor.

- Liver chemistries must be followed ***twice weekly for 'rechallenge'*** cases and ***once weekly for 'restart' cases*** for one month or for as long as clinically indicated following drug re-initiation. If the subject exhibits protocol-defined liver chemistry elevations, IP should be discontinued as protocol specified.

VSLC and the IRB/IEC must be informed of the subject's outcome following drug rechallenge or restart.

Rechallenge/restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting subject stopping criteria
- 2 = recurrent liver chemistry elevation meeting subject stopping criteria
- 3 = serious adverse event
- 4 = fatality

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-14.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatology. 2010;52:2216-22.

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

11.6. Appendix 6 Alternate RIF-Containing TB Treatment Regimens

The WHO-recommended first-line regimen for drug-sensitive TB is a combination regiment of isoniazid and RIF for six months, with ethambutol and pyrazinamide for the first two months. This regimen may be given daily or intermittently according to local or national guidelines. In case alternate TB treatments need to be considered due to tolerability/toxicity issues to one of the agents on the WHO-recommended first line regimen or due to antibiotic resistance, alternative TB treatment regimens are suggested below. The doses used should follow local or national guidelines. For additional information on alternate RIF-containing TB treatment regimens see Section 6.4.3.1.1. None of the alternate RIF-containing TB treatment regimens listed below should be used as the first-line TB treatment.

- **Regimen 1 (omitting pyrazinamide):** isoniazid, RIF, and ethambutol for 2 months, followed by RIF and isoniazid, for 7 months (9 months in total) [BTA, 1982; BTS, 1984; Slutkin, 1988].
- **Regimen 2 (omitting isoniazid):** RIF, pyrazinamide, ethambutol, and streptomycin for 2 months, followed by RIF and ethambutol for 7 months (9 months in total) [Babu, 1988].

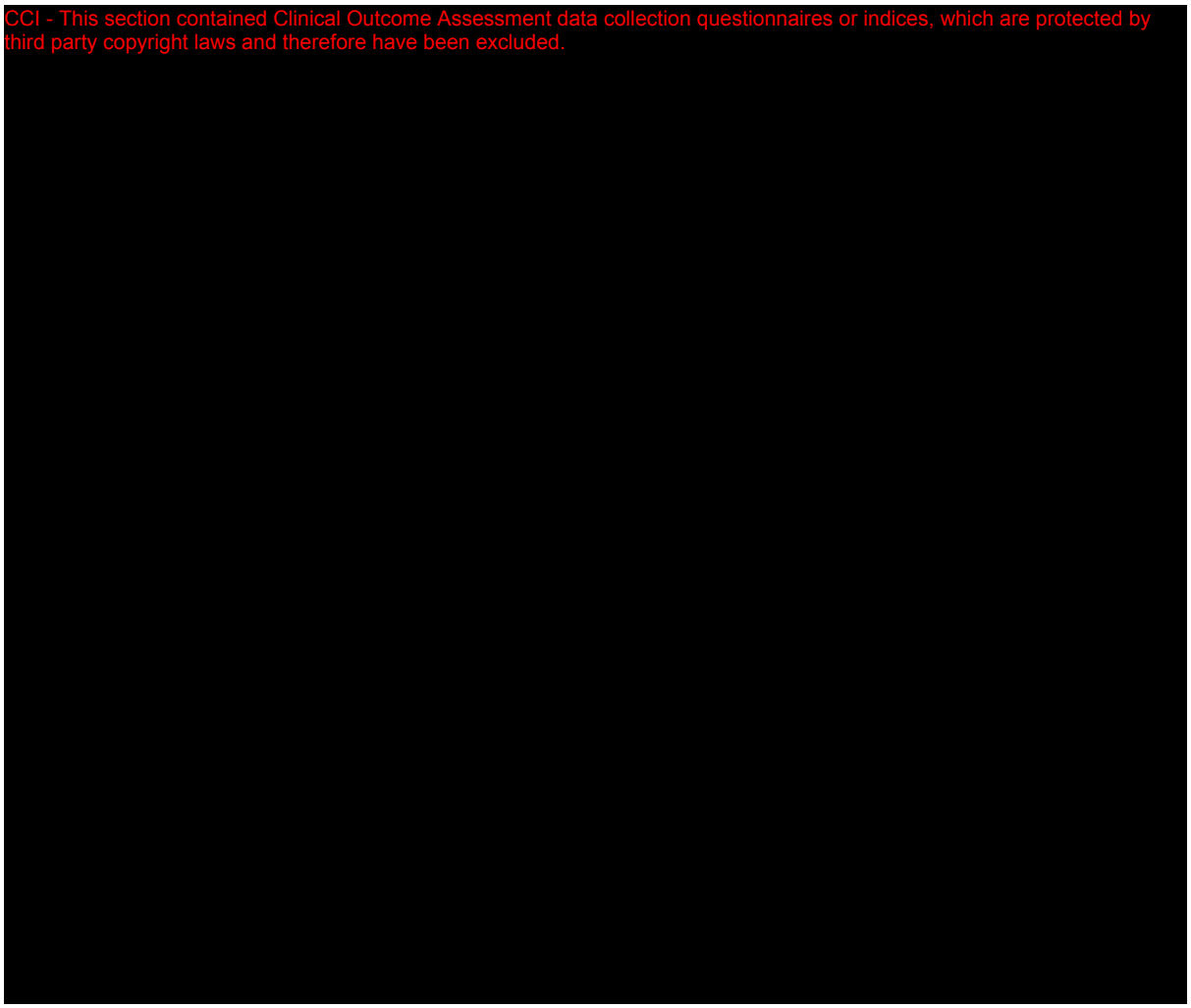
  The investigator may find Regimen 2 suitable in cases where isoniazid is found to have precipitated hepatotoxicity (i.e., in the course of TB drug re-introduction for Regimen 1) [BTS, 1984]. In which case, the investigator may choose to use the schedule suggested in Table 6. Guidance from a local expert should be sought.

  This is also a suitable regimen for use when the study subject is found to be infected with isoniazid-resistant TB. If the WHO first-line regimen was well-tolerated prior to the discovery of isoniazid-resistance, then it is reasonable for all drugs in Regimen 2 to be introduced simultaneously instead of using the schedule displayed Table 6.
- **Regimen 3 (omitting ethambutol)**: RIF, isoniazid, and pyrazinamide for 2 months, followed by RIF and isoniazid for 4 months [Combs, 1990].

  The investigator may choose to use Regimen 3 for those subjects who are intolerant to ethambutol (the principal adverse effect of ethambutol being optic neuritis). Provided other components of Regimen 3 have been well-tolerated, conversion from the WHO first-line regimen only requires that ethambutol be stopped. Otherwise, the schedule in Table 5 is suitable if there has been a drug-interruption and the investigator feels that a gradual reintroduction is required. Consultation from a local expert should be sought.

When making changes to TB treatment, national or local guidelines on the treatment of tuberculosis should always be followed and take precedence over the recommendations made in this section. Should the subject need to go on a regimen that excludes the use of RIF (e.g., for reasons of tolerability/toxicity or antibiotic resistance), then the subject will have to be withdrawn from the study. Further details describing withdrawal criteria are described in Section 4.5.

11.7. Appendix 7 Karnofsky Performance Status Scale



11.8. Appendix 8 Child-Pugh Classification

A subject is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 13). For subjects requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 13 Child-Pugh System

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy Grade 1[a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, SI units (µmol/L), Serum bilirubin, conventional units (mg/dL)	<34 <2	34 to 52 2 to 3	>52 >3
Serum albumin, SI units (g/L) Serum albumin, conventional units (mg/dL)	>35 >3.5	28 to 35 2.8 to 3.5	<28 <2.8
Prothrombin Time (seconds prolonged) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

a. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

References

Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg. 1997 Nov;3(6):628-637

Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:649-649.

11.9. Appendix 9: Pregnancy Information

11.9.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

11.9.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to ViiV/GSK/PPD within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to ViiV/GSK/PPD. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. GSK's central safety department also will forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.

- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to the Medical Monitor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study and must immediately discontinue study drug.

Reference

Hatcher RA, Trussell J, Nelson AL, et al, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

11.10. Appendix 10 Protocol Changes

11.10.1. Amendment 01: A global protocol amendment applicable to all participating countries:

Summary of Changes in Protocol Amendment 01 and Rationale

- Mailing address of study medical monitor was updated.
- Changes were made to the protocol text in the following sections to reflect the revision of the number of subjects to be randomized from ~125 to ~115 to alleviate enrolment difficulties and recruit the study in a timely manner. The reduced sample size will allow timely availability of the data while maintaining a high power for the sample size assumption. The changes were made in Protocol Summary Study Design Section, in Section 3.1, in Section 4.1, in Section 8.1.1 and in Section 8.2.1.
- Minor clarifications in the study conduct include clarification of the use of solid media for the 2 month TB culture to be preferred rather than mandated to be aligned with the original study intent to follow national recommendations for TB testing and management. Change was made in Section 3.1.1.
- Correction of the list of participating countries in Section 3.2 and Section 4.1.
- Minor clarifications on GeneXpert testing or equivalent validated test and the ability to perform the test at the Screening visit in alignment with the original the study design and intent and described in Section 3.1. Changes were made in Section 4.2 and Section 6.1.
- Addition of instructions for investigators on the new GSK/ViiV procedure requiring investigator to confirm and document their review of the SAE causality within 72 hours of submission of the SAE. Change was made in Section 6.4.14.
- Minor clarification and/or corrections of typographical errors were made in inclusion criteria 19 and 23 Section 4.3, in Section 6.4.14.2 and in Section 8.1 Table 9.
- Figure 6 in Appendix 5 was replaced by an identical and reformatted figure to improve readability.

List of Changes (Old deleted text shown as strike through and new text shown in bold)

- Page 3, SPONSOR INFORMATION PAGE last paragraph:

PPD MD, PhD
PPD
~~1800 Perimeter Park Drive, Suite 275~~**3900 Paramount Parkway, South Building, 3rd Floor, Office 352**

- Protocol Summary Study Design and Section 3.1 first and second paragraph:

This is a Phase IIIb, randomized, open-label study describing the efficacy and safety of DTG and EFV-containing ART regimens in HIV/TB co-infected patients. The study will be conducted in approximately **(±5%)** 1**1**~~2~~5 HIV-1 infected individuals who are ART-naïve with a CD4+ cell count ≥50 cells/mm^3 and newly diagnosed with confirmed pulmonary, pleural, or LN *Mycobacterium* TB (MTB) taking RIF-containing first-line TB treatment. Subjects should have confirmed RIF-sensitive MTB infection as determined by GeneXpert (or equivalent approved molecular test) or mycobacterial culture. Eligible subjects will be randomly assigned in a 3:2 ratio to receive DTG plus 2 NRTIs (approximately **69**~~75~~ subjects) or EFV plus 2 NRTIs (approximately **46**~~50~~ subjects).

- Section 3.1.2, 2nd Paragraph, 2nd sentence:

Sputum will be collected from subjects with pulmonary tuberculosis 2 months after initiating TB treatment (solid media culture testing is **preferred** ~~required~~).

- Section 3.2 Discussion of Design, 2nd paragraph, 1st sentence:

Adult subjects diagnosed (smear positive) and proven RIF-sensitive TB who are initiating TB treatment with HRZE will be recruited at sites in Brazil, Mexico, Russia, **Argentina, Peru,** South Africa~~, Malawi~~ and Thailand.

- Section 4.1, 1st and 2nd paragraph and Table:

A sufficient number of subjects will be screened in order to ensure that a total of approximately **(±5%)** 1**1**~~2~~5 subjects will be randomly assigned in a 3:2 ratio to DTG (approximately **69**~~75~~ subjects) and EFV (approximately **46**~~50~~ subjects), respectively.

Assuming 55% of subjects do not meet eligibility criteria, this will require the screening of approximately 2**5**~~7~~5 subjects. Subjects will be enrolled from Brazil, Mexico, Russia, **Argentina, Peru,** South Africa~~, Malawi,~~ and Thailand.

	Subjects
Screened	~2**5**~~7~~5
Randomized	~1**1**~~2~~5
Evaluable	~1**1**~~2~~5

- Section 4.2, Inclusion criteria 7 and 8:

3. New diagnosis of pulmonary, pleural, or LN tuberculosis based on identification of *Mycobacterium tuberculosis* using culture methods or GeneXpert **(or other approved molecular test)** on sputum or on samples collected by needle aspirate of pleural fluid or an affected LN;
4. RIF sensitivity of *Mycobacterium tuberculosis* either by culture or Gene Xpert (or other ~~validated~~ **approved** nucleic acid amplification test);

- Section 4.3, Exclusion criteria 19 and 23:

19. Any verified Grade 4 laboratory abnormality **with the exception of Grade 4 triglycerides. A single repeat test is allowed during the Screening period to verify a result**;

23. Platelet count <50**,**000/mm^3.

- Section 6.1, Table 2, row 8, column 1:

Perform GeneXpert or equivalent and/or Document GeneXpert or **equivalent** RIF-sensitive MTB.

- Section 6.4.14, new sentence added after Table 7:

The investigator will be required to confirm review of the SAE causality by ticking the 'For Investigators ONLY' box at the bottom of the eCRF page within 72 hours of submission of the SAE.

- Section 6.4.14.2, typo corrected:

If a clinically suspected case of HSR to ABC develops in subjects receiving ABC as part of their NRTI background regimen, and meets the definition of an ~~AE/~~SAE as described in Section 6.4.4, then, in addition to reporting the case as an SAE, the ABC HSR eCRF should also be completed within 1 week of the onset of the HSR (see Section 6.4.14).

- Section 8.1.1, Table 9, 3rd column, rows 2 to 5, typo corrected:

~~CD4+ cell count~~**HIV-1 RNA** <50 c/mL

- Section 8.1.1, 5th and last paragraph:

Assuming an 85% response rate for DTG at Week 48, a sample size of ~~75~~ **66 to 72** subjects in the DTG arm would have >~~90~~**85**% power to detect a response rate of greater than 70% **(Figure 4)**. Although the objective of the study is not to test a statistical hypothesis, the sample size has been chosen to provide an adequate number of subjects for assessing the antiretroviral activity of DTG.

- Section 8.2.1, 1st paragraph, 2nd sentence:

A sample size of **69**~~75~~ subjects has >90% power. Smaller samples (e.g., 6**5**~~9~~ or greater) have at least 8**6**~~8~~% power, which is relevant when assessing the primary endpoint in alternate analysis populations (i.e., modified ITT-E).

- Figure 6 in Appendix 5:

Figure 6 was reformatted.

11.10.2. Protocol changes for Amendment 02 from Amendment 01:

A global amendment applicable to all participating countries

Summary of Key Changes in Protocol Amendment 02 and Rationale

Changes were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defects in infants born to women with exposure to dolutegravir at the time of conception. Changes were also made to update references to the DTG IB to reflect the most current versions.

- The Risk Assessment table (Section 1.3.1, Table 1) was updated to include language regarding risk and mitigation of neural tube defects.
- The inclusion criteria (Section 4.2) were updated to align the pregnancy information with more recent protocols.
- The withdrawal criteria (Section 4.5) were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.
- The Time and Events table (Section 6.1, Table 2). was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy.
- A new Appendix was added detailing the modified list of highly effective methods for avoiding pregnancy in FRP and the collection of pregnancy data (Appendix 9, Section 11.9.1). The double barrier method of contraception, which does not meet updated GSK/ViiV criteria for a highly effective method, was excluded.

List of Specific Changes. Unless stated otherwise, new text is represented in bold font.

Section 1.3.1 Risk Assessment:

Added the following text:

DTG: Neural tube defects	**In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.**	**1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in**

		Females of Reproductive Potential (FRP) (see Appendix 9, Section 11.9.1) until the last dose of study medication. **2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded.** **3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and be withdrawn from the study.** **4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit.** **5. Pregnancy status is monitored at every study visit.**

Section 4.2 Inclusion Criteria

Previous Text

6. A female subject may be eligible to enter and participate in the study if she:

a is of non-childbearing potential defined as either postmenopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy, or bilateral oophorectomy or,

b is of childbearing potential, with a negative pregnancy test at both Screening and Day 1, and agrees to use one of the following methods of contraception to avoid pregnancy:

- Complete abstinence from intercourse from 2 weeks prior to administration of IP, throughout the study, and for at least 2 weeks after discontinuation of all study medications;
- Double-barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide);
- Approved hormonal contraception (see the SPM for a listing of examples of approved hormonal contraception) plus a barrier method while receiving RIF-containing TB treatment for subjects randomly assigned to the DTG arm, or approved hormonal contraception plus a barrier method for subjects randomly assigned to the EFV arm (regardless of RIF-containing TB treatment);
- Any intrauterine device (IUD) with published data showing that the expected failure rate is <1% per year (not all IUDs meet this criterion; see the SPM for an example listing of approved IUDs);
- Male partner sterilization prior to the female subject's entry into the study and this male is the sole partner for that subject;
- Any other method with published data showing that the expected failure rate is <1% per year.

Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of study drug. A childbearing potential female subject who starts the study using complete abstinence as her contraceptive method and decides to become sexually active must use the double barrier method either as a bridge to an approved hormonal contraception (if possible) or as a method of choice to be maintained from that moment onwards.

All subjects participating in the study should be counseled on safer sexual practices including the use of effective barrier methods (e.g. male condom/ spermicide).

Current text:

6. A female subject may be eligible to enter and participate in the study if she:

a. is of non-childbearing potential defined as either postmenopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy, or bilateral oophorectomy or,

b. is of childbearing potential, with a negative pregnancy test at both Screening and Day 1, and agrees to use one of the following methods of contraception to avoid pregnancy throughout the study and for at least two weeks after discontinuation of all study medication (see Appendix 9, Section 11.9):

- Complete abstinence from penile-vaginal intercourse from 2 weeks prior to administration of IP, throughout the study, and for at least 2 weeks after discontinuation of all study medications. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

- Approved hormonal contraception (see Appendix 9 Section 11.9 and the SPM for a listing of examples of approved hormonal contraception) plus a barrier method while receiving RIF-containing TB treatment for subjects randomly assigned to the DTG arm, and then regardless of use of a barrier method after discontinuation of RIF-containing TB treatment or approved hormonal contraception plus a barrier method for subjects randomly assigned to the EFV arm (regardless of RIF-containing TB treatment). Approved hormonal contraception including:
    - Combined oestrogen and progestogen oral contraceptive [Hatcher, 2011])
    - Contraceptive subdermal implant
    - Injectable progestogen [Hatcher, 2011]
    - Contraceptive vaginal ring [Hatcher, 2011]
    - Percutaneous contraceptive patches [Hatcher, 2011] ;
- Any intrauterine device (IUD); or intrauterine system
- Male partner sterilization with documentation of azoospermia *prior to the female subject's entry* into the study and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.;
- Any other method with published data showing that the expected failure rate is <1% per year.

Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of study drug. A childbearing potential female subject who starts the study using complete abstinence as her contraceptive method and decides to become sexually active must use the double barrier method either as a bridge to an approved hormonal contraception (if possible) or as a method of choice to be maintained from that moment onwards.

All subjects participating in the study should be counseled on safer sexual practices including the use of effective barrier methods (e.g. male condom/ spermicide).

Note: these contraceptive requirements do not apply to females of childbearing potential with same sex partners only, when this is their preferred and usual lifestyle.

Section 4.5 Withdrawal Criteria:

Previous text:

- Pregnancy (intrauterine), regardless of termination status of pregnancy.

Current text:

- Pregnancy (intrauterine), regardless of termination status of pregnancy. **As a reminder, females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.**

Section 6.1 Time and Events Table:

Inserted footnote r: **Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.**

Section 10: References

References to the DTG IB have been updated to add DTG IB version 11, supplement 01 and 02 as follows:

GlaxoSmithKline (GSK) Document Number RM2007/00683/11: Clinical Investigator's Brochure for GSK1349572 (Dolutegravir) Version 11. October 2017.

GlaxoSmithKline Document Number 2017N352880_00: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 01, 11 December 2017.

GlaxoSmithKline Document Number 2017N352880_01: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 02, June 2018.

Section 11.9: Appendix 9 Pregnancy

New Text:

11.9 Appendix 9: Pregnancy Information

11.9.1 Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]

- Percutaneous contraceptive patches [Hatcher, 2011]
- Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

11.9.2 Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to ViiV/GSK/PPD within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to ViiV/GSK/PPD. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. GSK's central safety department also will forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to the Medical Monitor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study and must immediately discontinue study drug.

Reference

Hatcher RA, Trussell J, Nelson AL, et al, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	ING117175: a Phase IIIb, randomized, open-label study of the safety and efficacy of dolutegravir or efavirenz each administered with two NRTIs in HIV-1-infected antiretroviral therapy-naïve adults starting treatment for rifampicin-sensitive tuberculosis

Compound Number: GSK1349572

Development Phase: IIIb

Effective Date: 21-MAR-2016

Protocol Amendment Number: 01

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2014N190475_00	2014-APR-24	Original
2014N190475_01	2016-MAR-21	Amendment No 1
Amended to include: change to the sample size from ~125 to ~115 (+/-5%) to alleviate the enrolment difficulties while maintaining a high power for the sample size assumption; clarification that the 2 month sputum TB culture to be performed on solid medium is preferred rather than mandated, correction of the list of participating countries, some minor clarifications to inclusion and exclusion criteria, clarification on the ability to perform GeneXpert testing (or equivalent validated test) at the Screening Visit, addition of investigator instructions on the new SAE review requirement in the eCRF, reformatting of Figure 6 to improve readability, and other minor clarifications and corrections of typographical errors.		

SPONSOR SIGNATORY

PPD

Kimberly Y. Sm[redacted]MD, MP[redacted]
Vice President Global Medical Strategy
ViiV Healthcare

3/24/16
Date

PPD

SPONSOR INFORMATION PAGE

Clinical Study Identifier: ING117175

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is implementing and managing all aspects of this study.

Sponsor Legal Registered Address:

ViiV Healthcare
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK
Telephone: PPD

Sponsor Contact Address

ViiV Healthcare
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Medical Monitor and Serious Adverse Events (SAE) Contact Information:

PPD MD, PhD
PPD
3900 Paramount Parkway, South Building, 3rd Floor, Office 352
Morrisville, NC 27560-8408
Phone: PPD
Fax: PPD
PPD

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number ING117175:

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
BUN	Blood urea nitrogen
c/mL	Copies/milliliter
CDC	Centers for Disease Control and Prevention
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
C-SSRS	Columbia-Suicidality Severity Rating Scale
CI	Confidence interval
CPK	Creatine phosphokinase
CrCL	Creatinine clearance
CYP	Cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DHHS	United States Department of Health and Human Services
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DRV	Darunavir, Prezista
DRV/r	Darunavir + Ritonavir
DTG	Dolutegravir
ECG	Electrocardiograph
eCRF	Electronic case report form
EFV	Efavirenz, Sustiva
FDA	US Food and Drug Administration
FTC	Emtricitabine, Emtriva
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INI	Integrase inhibitor
INR	International normalized ratio
IP	Investigational product

IRB	Institutional Review Board
IRIS	Immune reconstitution inflammatory syndrome
ITT	Intent-to-treat
ITT-E	Intent-to-treat-exposed
IVRS	Interactive voice response system
LDL	Low-density lipoprotein
LN	Lymph node
mg	Milligram
MITT-E	Modified intent-to-treat
mL	Milliliter
MTB	*Mycobacterium tuberculosis*
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OLE	Open-label extension
PCR	Polymerase chain reaction
PGx	Pharmacogenetic
PI	Protease inhibitor
PK	Pharmacokinetic
PRO	Protease
PSRAE	Possible suicidality-related adverse event
PT	Prothrombin time
RAL	Raltegravir, Isentress
RAP	Reporting and analysis plan
RIF	Rifampicin
RNA	Ribonucleic acid
RT	Reverse transcriptase
SAE	Serious adverse event
SPM	Study Procedures Manual
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate, Viread
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine, Truvada
TMP-SMX	Trimethoprim-sulfamethoxazole
ULN	Upper limit of normal
VSLC	ViiV Safety and Labeling Committee
WHO	World Health Organization

Trademark Information

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM
KIVEXA
TIVICAY
TRIZIVIR
ZIAGEN

Trademarks not owned by ViiV Healthcare
Atripla
Complera
Efavirenz
Emtriva
GeneXpert
GenoSure
Isentress
MedDRA
Monogram Biosciences
PhenoSense
Quest Diagnostics
SAS
Standard Phenosense

PROTOCOL SUMMARY

Rationale

Study ING117175 is being conducted to assess the antiretroviral activity of a dolutegravir (DTG)-containing regimen (50 mg twice-daily during tuberculosis [TB] treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once-daily, with 2 nucleoside reverse transcriptase inhibitors [NRTIs]) in antiretroviral therapy (ART)-naïve patients with human immunodeficiency virus (HIV)-1 infection taking rifampicin (RIF)-containing first-line treatment for pulmonary, pleural, and lymph node (LN) RIF-sensitive TB. Safety, TB-associated immune reconstitution inflammatory syndrome (IRIS), and tolerability will also be explored. This study is designed to assess the antiviral activity of DTG and efavirenz (EFV) ART-containing regimens through 48 weeks.

Objectives

Primary Objective

To assess the antiviral activity at 48 weeks of a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily, with 2 NRTIs) in ART-naïve patients with HIV-1 infection taking RIF-containing TB treatment.

Secondary Objectives

- To assess the antiviral activity of DTG and EFV both administered with 2 NRTIs at Week 24;
- To assess the antiviral activity of EFV administered with 2 NRTIs at Week 48;
- To evaluate immunological activity (CD4+ lymphocyte [CD4 counts]) at Week 24 and Week 48;
- To evaluate the safety, TB-associated IRIS, and tolerability in subjects treated with a DTG- or EFV-based regimen concurrently with treatment for TB over time;
- To assess the development of HIV-1 resistance in subjects who meet confirmed virologic withdrawal criteria over 24 and 48 weeks.

Tertiary Objectives

- To evaluate the incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death) over time;
- To describe rates of TB treatment success (using the World Health Organization [WHO] definition) for all subjects;
- To describe the proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment;

- To evaluate concentrations of DTG and EFV using sparse sampling and to characterize DTG pharmacokinetics and variability during and post TB treatment and to explore the association between DTG and EFV concentrations and antiviral activity at Week 24 and Week 48.

Study Design

This is a Phase IIIb, randomized, open-label study describing the efficacy and safety of DTG and EFV-containing ART regimens in HIV/TB co-infected patients. The study will be conducted in approximately (+/- 5%) 115 HIV-1 infected individuals who are ART-naïve with a CD4+ cell count ≥50 cells/mm^3 and newly diagnosed with confirmed pulmonary, pleural, or LN *Mycobacterium* TB (MTB) taking RIF-containing first-line TB treatment. Subjects should have confirmed RIF-sensitive MTB infection as determined by GeneXpert (or equivalent approved molecular test) or mycobacterial culture. Eligible subjects will be randomly assigned in a 3:2 ratio to receive DTG plus 2 NRTIs (approximately 69 subjects) or EFV plus 2 NRTIs (approximately 46 subjects). The dual NRTI backbone will be selected by the investigator in accordance with local standard of care and per current WHO or national guidelines for the treatment of HIV/TB co-infected adults. Subjects randomization will be stratified by screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). An interim analysis will be conducted when all subjects complete their Week 24 visit, the primary Week 48 analysis will be conducted when the last subject completes the Randomized Phase, and a final end-of-study analysis will be conducted when the final subject randomly assigned to DTG has transitioned from the Open-Label Extension (OLE) to commercial supplies of DTG or is withdrawn for the study.

This study will include a Screening Period, a Randomized Phase (Day 1 to Week 48 plus a 4-week extension), and a DTG OLE.

Only protocol-defined dose reductions, modifications, or changes in the frequency of any components of each HIV regimen or TB treatment will be allowed at any time in this study, including during the Screening Period.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be promptly communicated to the study medical monitor.

Study Endpoints/Assessments

The primary endpoint for this study will be the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population in the DTG arm.

Secondary Efficacy Endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the EFV arm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related adverse event (AE), safety stopping criteria, or lack of efficacy);
- Changes from baseline in CD4+ counts at Week 24 and Week 48.

Tertiary Efficacy Endpoints

- Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses, and death);
- Proportion of subjects with TB treatment success (using the WHO definition);
- Proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment.

Safety endpoints will include: incidence and severity of AEs and laboratory abnormalities, proportion of subjects who discontinue treatment due to AEs, and proportion of subjects with TB-associated IRIS.

Pharmacokinetic endpoint will include an evaluation of concentrations of DTG and EFV measured at Weeks 8, 24, 36, and 48 using sparse sampling.

Virologic endpoint will be the incidence of treatment-emergent genotypic and phenotypic resistance to DTG, EFV, and other on-study ART in subjects meeting confirmed virologic withdrawal criteria over 24 and 48 weeks.

1. INTRODUCTION

1.1. Background

Approximately 14 million individuals worldwide are estimated to be dually infected with human immunodeficiency virus (HIV) and tuberculosis (TB). The yearly incidence of TB infection is about 10% among patients with HIV and TB is the most common cause of death in patients with HIV worldwide. HIV and TB co-infection have profound effects on the host's immune system. Recent studies evaluating the optimal timing for initiation of antiretroviral therapy (ART) in patients requiring treatment for active TB demonstrated a survival benefit for starting ART soon after TB treatment initiation rather than waiting until TB treatment completion. More specifically, current United States Department of Health and Human Services (DHHS) guidelines [DHHS, 2014] suggest that for patients with a CD4+ cell count <50 cells/mm^3, ART should be started within 2 weeks of starting TB treatment; for patients with a CD4+ cell count ≥50 cells/mm^3, ART should be started within 2 months of starting TB treatment [Török, 2011]. British guidelines suggest starting as soon as possible for patients with a CD4+ cell count ≤100 cells/mm^3 [British HIV Association (BHIVA) Guidelines, 2011]. As a result of the aforementioned studies and guidelines, there is an increase in the number of co-infected individuals being treated concurrently.

Currently, rifamycins (such as rifampicin [RIF]) serve as the cornerstone of TB therapy because of their unique sterilizing activity. No drug can adequately substitute for rifamycins in the TB regimen; if rifamycins cannot be used, treatment duration must be substantially prolonged (from 6 months to 9 to 24 months in most cases). TB treatment is given in 2 stages: during the first 2 months (intensive phase), patients with RIF-sensitive TB receive isoniazid (H), RIF (R), pyrazinamide (Z), and ethambutol (E) (HRZE), and during the subsequent 4 months (TB treatment continuation phase), patients receive isoniazid and RIF (HR). Some national guidelines recommend a TB treatment continuation phase of HR extended to 7 months in HIV and TB co-infected patients.

Rifampicin is the most commonly used rifamycin for TB treatment. It is a potent inducer of cytochrome P450 enzyme activity. By activating the pregnane X receptor (PXR), RIF can induce multiple metabolic enzymes, including cytochrome P450 (CYP) isoenzyme 3A (CYP3A), other CYP enzymes, Phase II drug-metabolizing enzymes, UDP-glucosyltransferases, sulfonyltransferases, and drug transporters. Since most protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) used to treat HIV are metabolized by CYP3A, induction of CYP3A by RIF can lead to reduced serum concentrations of antiretroviral drugs with risk of treatment failure or emergence of resistance to antiretroviral drugs. Nucleoside reverse transcriptase inhibitor (NRTI) concentrations, though, are not reduced by RIF in a clinically meaningful way. In patients who must be treated with RIF-containing TB therapy and require concurrent ART, efavirenz (EFV)-based ART can be used safely and effectively [Boulle, 2008; DHHS, 2013; WHO, 2010]. However, because the side effect profile of EFV (which includes treatment-related rash, CNS effects, and liver enzyme elevations) overlaps with the adverse effect profile of HRZE therapy, management of toxicity is complex. Integrase inhibitors (INI) may offer an important alternative to EFV-based therapy in TB co-

infected patients. Although the BHIVA guidelines recommend an increased dose of EFV of 800 mg for HIV/TB co-infected patients [BHIVA Guidelines, 2011], the DHHS, Centers for Disease Control and Prevention (CDC), and WHO TB guidelines do not recommend a dose increase of EFV [DHHS, 2014; WHO, 2010; CDC, 2013], because the evidence that RIF treatment impacts HIV antiviral responses with EFV-based combination ART is weak. In addition, among the minority of patients with lower levels of EFV during TB therapy, EFV concentrations remain above the required levels for adequate antiviral activity and an even lower dose of EFV has recently been shown to be effective. In the ENCORE study, the 400-mg once-daily dose of EFV in combination with tenofovir/emtricitabine (TDF/FTC) has been shown to be non-inferior to EFV 600 mg once daily with TDF/FTC at Week 48 in ART-naive patients [ENCORE1 Study Group, 2014].

Further, for those with contraindications or resistance to NNRTIs, there are few treatment options, as RIF cannot be used safely or effectively with PIs, even with dose adjustment. Substitution of rifabutin (RBT) for RIF is a reasonable TB treatment option for HIV/TB co-infected adults; however, because RBT is metabolized by CYP3A4, it requires bidirectional dose adjustment when given with PIs, and the optimal RBT dosing frequency is unknown. In addition, access to rifabutin is difficult in most resource-limited settings. The same potential drug interaction problem may occur when treating HIV/TB co-infection using recently developed antituberculosis drugs such as the diarylquinoline antimycobacterial drug bedaquiline, as exposure to this drug may be reduced during co-administration with inducers of CYP3A4 and increased during co-administration with inhibitors of CYP3A4 [Sirturo Product Information, 2013]. An antiretroviral drug that could be taken with an NRTI backbone and be used safely and effectively with RIF in the treatment of HIV/TB co-infection without the need for adjustments to the patient's TB regimen would give physicians and patients an important treatment option.

1.2. Rationale

In a Phase II open-label, randomized clinical study, the HIV INI raltegravir (RAL) was shown to be a suitable antiretroviral drug alternative to EFV for HIV/TB co-infected patients undergoing TB therapy study after 48 weeks of treatment (Grinsztejn, 2014). These results support the investigation of other INIs such as dolutegravir (DTG) in HIV/TB co-infection.

DTG is approved in the United States, Canada, the EU, Brazil, and in other countries, and is under review with other countries' regulatory agencies. Two Phase III studies, ING114467 (SINGLE) and ING113086 (SPRING-2) evaluated safety and efficacy of DTG in HIV-infected adults who were ART-naïve. ING114467 (SINGLE) evaluated the safety and efficacy of DTG 50 mg once daily plus FDC abacavir/lamivudine (ABC/3TC) 600 mg/300 mg compared with Atripla (EFV/FTC/TDF). Following 48 weeks of treatment, 88% of the subjects receiving DTG (50 mg once daily plus ABC/3TC) compared with 81% of the subjects receiving EFV/FTC/TDF had plasma HIV-1 RNA levels of <50 copies/mL; test for superiority had a p=0.003 [Walmsley, 2013]. ING113086 (SPRING-2) evaluated antiviral efficacy of DTG 50 mg once daily plus dual NRTI. After 48 weeks of treatment, 88% of the subjects receiving DTG (50 mg once daily plus TDF/FTC 300 mg/200 mg or ABC/3TC 600 mg/300 mg) compared with 85%

of those taking RAL (400 mg twice daily plus TDF/FTC 300 mg/200 mg or ABC/3TC 600 mg/300 mg) had plasma HIV-1 RNA levels of <50 copies/mL [Raffi, 2013a]. DTG was shown to be efficacious and non-inferior to RAL in combination with a dual NRTI. Non-inferiority between DTG and RAL was also demonstrated at Week 96 [Raffi, 2013b]. DTG 50 mg twice daily has also been studied in patients with INI-resistant virus in the VIKING and VIKING-3 studies and shown to be effective and well tolerated, with a safety profile comparable to that of DTG 50 mg once daily [Eron, 2013; Castagna, 2014]. Rates of discontinuation due to adverse events (AEs) were ≤2% in the DTG 50 mg once a day arms of the ART-naïve studies and ≤4% in the treatment-experienced population in the VIKING-3 study on DTG 50 mg twice a day with an optimized background regimen.

DTG is primarily metabolized by UGT1A1 with CYP3A4 as a minor route, and both enzymes are induced by RIF. Therefore a Phase I open-label, 3-period, fixed-sequence study was conducted in healthy, HIV-seronegative subjects, evaluating the pharmacokinetic (PK) and safety of DTG given alone at a dose of 50 mg once daily to that of DTG given at a dose of 50 mg twice daily together with steady-state RIF [Dooley, 2013]. Twice-daily DTG plus RIF achieved mean DTG concentrations that were 20%-33% higher than once-daily DTG dosing alone. Specifically, the geometric mean ratio for the 24-hour area under the time-concentration curve (AUC0-24), comparing DTG twice daily plus RIF with DTG once daily, was 1.33 (90% confidence interval [CI] 1.14 to 1.54). The GMR for the trough concentration at the end of the dosing interval (Cτ) was 1.22 (90% CI 1.01 to 1.48). There were no discontinuations for AEs and any Grade 3 or higher AEs. In summary, in this Phase I study, DTG at 50 mg twice daily given together with standard-dose RIF was well-tolerated and resulted in DTG concentrations similar to those of DTG 50 mg given once daily alone. Based on these results and as specified in the DTG prescribing information, the dose selection of twice-daily DTG 50 mg plus dual NRTI tablet during TB treatment was selected. The twice-daily regimen will be maintained for 2 weeks following discontinuation of TB treatment in order to eliminate (i.e., washout) the effects of RIF on the induction of UGT1A1 and CYP3A4; thereafter; once-daily DTG 50 mg with the same NRTI backbone will be administered through Week 48.

ART regimens using DTG 50 mg twice daily may represent a new treatment option for TB-infected patients who require concurrent treatment for HIV infection. This study will examine the use of DTG-based regimen among patients with HIV/TB co-infection.

1.3. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG can be found in the most current version of the Investigator's Brochure (IB) [GlaxoSmithKline Document Number RM2007/00683/07]. The following section outlines the risk assessment and mitigation strategy for the use of DTG as described in this protocol.

The approved country product labels should be referenced for RIF and all other components of the TB regimen, NRTIs, and EFV.

1.3.1. Risk Assessment

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Considerations when using DTG are presented in Table 1.

Table 1 Considerations When Using DTG

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG] Refer to IB for additional information on DTG		
Hypersensitivity and Rash	HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme were reported.	Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 4.3). Specific/detailed toxicity management guidance is provided for HSR (Section 6.4.3.5) and rash (Section 6.4.3.8). The subject informed consent form includes information on this risk and the actions subjects should take in the event of a rash or associated signs and symptoms.
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For subjects with hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG- containing ART contributed to significant elevations in liver chemistries. Drug-induced liver injury is a well-described adverse outcome of TB treatment. The risk of DILI from TB treatment is higher if the subject is also co-infected with HIV.	Subjects meeting either of the following criteria during the Screening Period are excluded from participating (Section 4.3). • Alanine aminotransferase (ALT) ≥2 times the upper limit of normal (ULN) • Subjects with an anticipated need for hepatitis C virus (HCV) therapy during the Randomized Phase (Day 1 to Week 48 plus a 4-week treatment extension) Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 6.4.3.1).
Theoretical serious drug interaction with dofetilide and pilsicainide	Co-administration of DTG may increase dofetilide/pilsicainide plasma concentration via inhibition of organic cation transporter 2 (OCT2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 5.6.2).
GI intolerance	Non-clinical studies showed upper and lower GI toxicity, including vomiting, diarrhoea and gastric erosions observed in monkey toxicology studies (thought to be related to local and not systemic toxicity). Mild to moderate GI intolerance (mainly diarrhoea and nausea) is associated	Routine monitoring of GI symptoms will be performed.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG] Refer to IB for additional information on DTG		
	with DTG treatment in a small proportion of subjects; however there were no indications of an increased risk for peptic ulcers or serious erosions.	
Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT2 receptor. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (Section 6.4.3.4).
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviours are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar or favourable compared with other ART. The reporting rate for insomnia was statistically higher for blinded DTG+ABC/3TC compared with EFV/TDF/FTC in ING114467; however, this was not duplicated in any other Phase IIb/III study conducted with DTG.	Subjects who in the investigator's judgment, poses a significant suicidality risk, are excluded from participating (Section 4.3). Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality will be monitored during this study. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour (Section 6.4.10).
Creatine phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	Specific detailed toxicity management guidance is provided for subjects who develop Grade 3 to 4 CPK elevations (Section 6.4.3.7).
Increased occurrence of immune reconstitution inflammatory syndrome (IRIS)	With rapid HIV-1 RNA decline and early recovery of CD4+ cell counts there could theoretically, be an increase in cases of IRIS. Based on medical adjudication of IRIS-like events in ING111762, ART-experienced (INI-naïve) subjects with hepatitis C virus co-infection receiving DTG may be at greater risk for IRIS than those receiving RAL, due to improved HIV virologic and immunologic responses with DTG compared with RAL.	Subjects will be monitored for signs and symptoms of TB-associated IRIS. Definitions on criteria for diagnosing these cases are provided in Section 6.4.6. Subjects will also have frequent liver chemistry monitoring. Robust liver chemistry stopping criteria and liver event follow-up assessments are included.

3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ALT = alanine aminotransferase, CPK = creatine phosphokinase, DILI = drug induced liver injury, DTG = dolutegravir, EFV = efavirenz, FTC = emtricitabine, GFR = glomerular filtration rate, GI = gastrointestinal, HCV = hepatitis C virus, IRIS = immune reconstitution inflammatory syndrome, TDF = tenofovir, OCT2 = organic cation transporter 2, ULN = upper limit of normal

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for HIV-infected patients). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of investigational product (IP), and will be followed to resolution as per sponsor's standard medical monitoring practices. Clinical safety data will be routinely reviewed in GSK Safety Review team meetings. This will include in-stream review of data from this clinical trial on a routine basis, review of aggregate data on a protocol and program basis when available, and review of competitor data from the literature.

Events will be monitored using SAE reports and alerts for Grade 3/4 laboratory toxicities (according to the Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity grading for HIV-infected patients as described in Section 11.3). Serious/severe events will be managed appropriately including, but not limited to, IP being withdrawn, and will be followed to resolution by the medical monitor. Further information on SAE reporting is described in Section 6.4.14.

Clinical safety data will be routinely reviewed in GSK Safety Review team meetings. This will include in-stream review of data from this clinical trial on a routine basis; review of aggregate data on a protocol and program basis when available; and review of competitor data from the literature.

1.3.2. Benefit Assessment

Early initiation of HAART together with HRZE therapy significantly reduces mortality in HIV-TB co-infected patients [DHHS, 2013]. Both EFV-based and RAL-based therapy have been shown to be effective for HIV/TB co-infected patients; in the REFLATE study, 48 week success rates with RAL 400 twice daily was 76% (95% CI 65-88), 63% (95% CI 49-76) with RAL 800 mg twice daily; and 67% (95% CI 54-80) with EFV, with no significant differences among the groups. Thirty-three percent to 37% of the subjects in each treatment group developed Grade 3 or higher AEs. These results suggest the possibility for improvements in treatment outcomes.

The safety profile for DTG 50 mg once daily was comparable to RAL and darunavir + ritonavir (DRV/r) and generally favorable to the EFV/TDF/FTC STR (Atripla) in both ART-naïve and ART-experienced (INI-naïve) patients (studies ING113086 [SPRING-2], ING111762 [SAILING], ING114915 [FLAMINGO] and ING114467 [SINGLE]). The most frequently observed AEs across patient populations were diarrhea, nausea, and headache, which were generally Grade 1 or 2 in severity, and typically did not lead to discontinuation from studies. With regards to antiviral efficacy, in treatment-naïve HIV-infected adult subjects, DTG 50 mg once daily was shown to be non-inferior to RAL in combination with a dual NRTI background regimen (SPRING-2). In study ING114915 (FLAMINGO), virologic suppression (HIV-1 RNA <50 c/mL) in the DTG arm (90%) was statistically superior to the DRV/r arm (83%) at Week 48. When used in combination with ABC/3TC, DTG was shown to be superior to EFV/TDF/FTC, a result driven by better tolerability of the DTG based regimen (SINGLE). In study ING111762 (SAILING), 71% of in INI-naïve ART-experienced patients receiving DTG achieved undetectable viral load (<50 c/ml) compared with 64% of those taking RAL at Week 48, reaching the threshold for statistical superiority [Cahn, 2013]. In the ING112574 (VIKING-3) study, DTG administered at 50 mg twice daily was demonstrated to be safe and effective in patients with INI resistance [Castagna, 2014, GlaxoSmithKline Document Number 2013N177327_00].

Study participants may also benefit from the medical tests and screening procedures performed as part of the study.

1.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with the DTG are justified by the anticipated benefits that may be afforded to HIV-1/TB co-infected ART-naïve adults.

2. OBJECTIVES

2.1. Primary Objective

To assess the antiviral activity at 48 weeks of a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily, with 2 NRTIs) in ART-naïve patients with HIV-1 infection taking RIF-containing TB treatment.

2.2. Secondary Objectives

- To assess the antiviral activity of DTG and EFV both administered with 2 NRTIs at Week 24;
- To assess the antiviral activity of EFV administered with 2 NRTIs at Week 48;
- To evaluate immunological activity (CD4+ lymphocyte [CD4 counts]) at Week 24 and Week 48;
- To evaluate the safety, TB-associated immune reconstitution inflammatory syndrome (IRIS), and tolerability in subjects treated with a DTG- or EFV-based regimen concurrently with treatment for TB over time;
- To assess the development of HIV-1 resistance in subjects who meet confirmed virologic withdrawal criteria over 24 and 48 weeks.

2.3. Tertiary Objectives

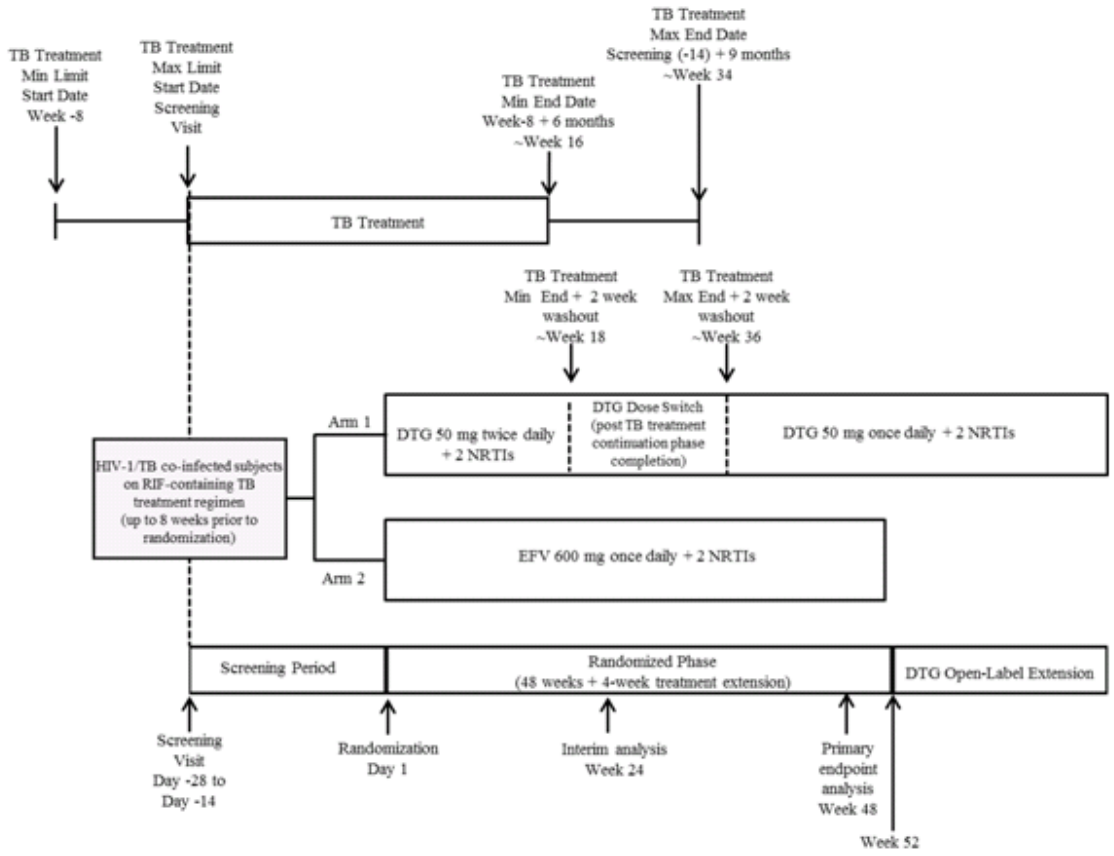
- To evaluate the incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death) over time;
- To describe rates of TB treatment success (using the WHO definition [WHO, 2010]) for all subjects;
- To describe the proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment;
- To evaluate concentrations of DTG and EFV using sparse sampling and to characterize DTG PK and variability during and post TB treatment and to explore the association between DTG and EFV concentrations and antiviral activity at Week 24 and Week 48.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a Phase IIIb, randomized, open-label study describing the efficacy and safety of DTG and EFV-containing ART regimens in HIV/TB co-infected patients. The study will be conducted in approximately (+/-5%) 115 HIV-1 infected individuals who are ART-naïve with a CD4+ cell count ≥50 cells/mm^3 and newly diagnosed with confirmed pulmonary, pleural, or LN *Mycobacterium* TB (MTB) taking RIF-containing first-line TB treatment. Subjects should have confirmed RIF-sensitive MTB infection as determined by GeneXpert (or equivalent approved molecular test) or mycobacterial culture.

Figure 1 Study Schematic



DTG = dolutegravir; EFV = efavirenz; max = maximum; mg = milligram; min = minimum; NRTI = nucleoside reverse transcriptase inhibitor; NTP = National TB Control Program; RIF = rifampicin; TB = tuberculosis
Note: TB treatment including isoniazid, RIF, pyrazinamide, and ethambutol will be provided at standard doses by the NTP under program conditions.

Eligible subjects will be randomly assigned in a 3:2 ratio to receive DTG plus 2 NRTIs (approximately 69 subjects) or EFV plus 2 NRTIs (approximately 46 subjects). The dual NRTI backbone will be selected by the investigator in accordance with local standard of care and per current WHO or national guidelines for the treatment of HIV/TB co-infected adults. Subjects randomization will be stratified by screening plasma HIV-1 RNA

(≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). An interim analysis will be conducted when all subjects complete their Week 24 visit, the primary Week 48 analysis will be conducted when the last subject completes the Randomized Phase, and a final end-of-study analysis will be conducted when the final subject randomly assigned to DTG has transitioned from the Open-Label Extension (OLE) to commercial supplies of DTG or is withdrawn for the study.

This study will include a Screening Period, a Randomized Phase (Day 1 to 48 weeks plus a 4-week extension), and a DTG OLE.

Only protocol-defined dose reductions, modifications, or changes in the frequency of any components of HIV regimen or TB treatment will be allowed at any time in this study, including during the Screening Period (Section 5.1.5).

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 2), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be promptly communicated to the study medical monitor.

3.1.1. Screening Period

TB diagnosis and confirmation of RIF-sensitive MTB infection must be performed locally. If the result confirming MTB infection is not available before the subject is screened, the assessment can be performed simultaneously in order to screen the subject for the study. Subjects with RIF-resistant TB are not eligible to enter the study. GeneXpert or other molecular test result is required to rule out RIF resistance prior to entry. Mycobacterial culture may be used to confirm RIF-sensitivity (as an alternative to GeneXpert or molecular testing) provided the culture results are available prior to randomization. The 14-day Screening Period may be extended to 28 days to allow receipt of all screening assessment results and to accommodate scheduling. Subjects are allowed to re-screen for this study one time; this will require a new subject ID number. A single repeat test (retest) per analyte or assessment is allowed during the Screening Period to determine eligibility, except for HIV drug resistance testing.

3.1.2. Randomized Phase (Day 1 to Week 48 plus 4-Week Extension)

As soon as all screening results are available, subjects who fulfill all eligibility requirements will be randomly assigned in a 3:2 ratio to receive either DTG or EFV-containing regimens, respectively. DTG or EFV regimens will be started up to 8 weeks after TB treatment initiation and will continue for 48 weeks, plus a 4-week extension.

TB treatment consisting of HRZE for 2 months (i.e., TB treatment intensive phase) followed by HR for 4 or 7 months (i.e., TB treatment continuation phase) will be administered according to local guidelines with TB treatment provided by the National TB Control Programs (NTP) in accordance with national guidelines. Sputum will be collected from subjects with pulmonary tuberculosis 2 months after initiating TB treatment (solid media culture testing is preferred). Sputum will also be collected at

4 months, 6 months, and 9 months (for subjects who receive TB treatment for 9 months) for smear and culture, for as long as the subject is able to produce sputum. Sputum samples are not required from subjects diagnosed only from pleural or LN aspirates that do not also have pulmonary disease. The same laboratory and method of MTB culture must be used during the study.

Subjects assigned to Arm 1 will receive DTG 50 mg twice-daily with 2 NRTIs until 2 weeks after TB therapy is completed then they will receive DTG 50 mg once daily (with the same NRTI backbone) through the end of the Randomized Phase. Subjects randomized to Arm 2 will receive EFV 600 mg once daily plus 2 NRTIs through the end of the Randomized Phase. The NRTI background regimen selected by the investigator must be determined and documented prior to randomization and should be composed of 2 NRTIs in accordance with the local standard of care and per the WHO or national treatment guidelines for HIV/TB co-infection. Following Day 1, no changes or intensification of background regimen will be permitted prior to meeting confirmed virologic withdrawal criteria or Week 52, with the exception of one allowed background NRTI change for management of drug toxicity as described in Section 6.4.3.

Subjects randomization will be stratified by screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). DTG and EFV will be administered in an open-label fashion throughout the Randomized Phase.

During the Randomized Phase, subjects will attend the clinic at Baseline/Day 1 and at Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

Following the Week 48 visit, subjects will remain on their DTG or EFV-containing regimen for an additional 4 weeks. All subjects will attend the Week 52 visit, although only those with a viral load of ≥50 c/mL at Week 48 will have their viral load confirmed by an assessment at the Week 52 visit. This treatment extension will allow for a more accurate assessment of treatment response for the Week 48 analysis window, as transient increases of HIV-1 RNA levels ≥50 c/mL will not be classified as virologic failure.

To determine DTG and EFV concentrations, sparse plasma samples will be collected at Weeks 8, 24, 36, and 48 in as many subjects as possible. If a subject meets virologic withdrawal criteria, HIV-1 resistance testing will be performed to assess treatment emergent mutations for INIs, NNRTIs, and NRTIs.

3.1.3. DTG Open-Label Extension

Only those subjects randomized to receive DTG plus 2 NRTIs will enter into the DTG OLE.

If DTG is locally approved and commercially available when a subject successfully completes the Randomized Phase, the subject will be considered to have completed the study (see Section 3.1.5) and will need to have alternate arrangements in place to access DTG and NRTIs. If DTG is not locally approved and commercially available when a subject successfully completes the Randomized Phase, he/she will have the opportunity

to enter into the DTG OLE. During the DTG OLE, subjects will be supplied with DTG until it is locally approved and commercially available, the subject no longer derives clinical benefit, or the subject meets a protocol-defined reason for discontinuation. Subjects who enter the DTG OLE will be monitored accordingly every 12 weeks.

3.1.4. Study Completion

Subjects are considered to have completed the study if they satisfy one of the following:

- Randomized to EFV plus 2 NRTIs and completed the Randomized Phase including the Week 52 visit;
- Randomized to DTG plus 2 NRTIs and completed the Randomized Phase including the Week 52 visit; and did not enter the DTG OLE;
- Randomized to DTG plus 2 NRTIs, completed the Randomized Phase, including the Week 52 study visit, and entered and completed the DTG OLE (defined as remaining on study until commercial supplies of DTG become locally available).

3.1.5. Follow-up

Subjects with ongoing AEs or laboratory abnormalities will attend a Follow-up visit approximately 4 weeks after their last dose of investigational product (IP) (DTG or EFV). Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality). The Follow-up visit is not required for successful completion of the study.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2. Discussion of Design

This randomized, open-label, multicenter, parallel group study design aims at assessing DTG antiviral activity in a sufficient number of subjects to demonstrate a clinically acceptable level of activity in HIV/TB co-infected patients receiving concomitant TB therapy.

Adult subjects diagnosed (smear positive) and proven RIF-sensitive TB who are initiating TB treatment with HRZE will be recruited at sites in Brazil, Mexico, Russia, Argentina, Peru, South Africa and Thailand. These areas were selected based on epidemiology which suggests high rates of HIV and TB co-infection (WHO). Global Tuberculosis Report, 2013).

The primary endpoint, proportion of subjects at Week 48 with plasma HIV-1 RNA <50 c/mL, is a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression.

Efavirenz-based regimens are the preferred regimens for patients with HIV and TB coinfection because of complications arising from drug interactions with other agents. In this study, the use of EFV as the active control in (HIV) therapy-naïve patients with TB is justified based on its indication as an appropriate agent as first-line therapy in treatment-naïve HIV-1-infected adults in WHO, CDC, and EACS guidelines.

DTG has been extensively studied in Phase II and Phase III studies in a variety of HIV-1 patient populations (e.g., treatment-naïve, treatment-experienced [integrase naïve], and treatment-experienced [integrase resistant]). DTG with dual NRTI therapy has not been evaluated in HIV/TB co-infected subjects taking RIF. This study will provide important information regarding the efficacy, safety and tolerability, incidence of TB-associated IRIS, and PK of DTG plus 2 NRTIs as a first-line ART regimen in HIV/TB co-infected subjects receiving concomitant TB therapy.

The use of DTG at the 50 mg twice-daily dose is in accordance with DTG global labeling information (i.e., United States and the EU) [DTG US Prescribing Information, 2013; EU SmPC, 2014] when dosed with RIF and is based on the results of the PK drug-drug interaction study with both drugs [Dooley, 2013]. The DTG 50 mg twice-daily dose is continued 2 weeks after completion of the TB treatment course, after which RIF enzyme induction would be minimal.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

A sufficient number of subjects will be screened in order to ensure that a total of approximately (+/-5%) 115 subjects will be randomly assigned in a 3:2 ratio to DTG (approximately 69 subjects) and EFV (approximately 46 subjects), respectively.

Assuming 55% of subjects do not meet eligibility criteria, this will require the screening of approximately 255 subjects. Subjects will be enrolled from Brazil, Mexico, Russia, Argentina, Peru, South Africa and Thailand.

	Subjects
Screened	~255
Randomized	~115
Evaluable	~115

The primary analysis will use all subjects in the intent-to-treat exposed (ITT-E) population, consisting of randomly assigned subjects who receive at least one dose of study drug. Since the intent is for all randomly assigned subjects to receive study drug, the number of evaluable subjects should equal the number randomized subjects.

Further details of sample size assumptions are found in Section 8.1.1.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GlaxoSmithKline (GSK) investigational product or other study treatment that may impact subject eligibility is provided in the IB.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following are study-specific eligibility criteria unless stated otherwise. In addition to these criteria, investigators must exercise clinical discretion regarding selection of appropriate study subjects, taking into consideration any local treatment practices or guidelines and Good Clinical Practice (GCP). Specifically, investigators must follow national treatment guidelines for ART initiation for HIV/TB co-infected adults. Investigators must also ensure that HIV care for study subjects is available and will be provided locally after study completion. Study completion is described in Section 3.1.4.

Eligible subjects must:

- Be able to understand and comply with protocol requirements, instructions, and restrictions,
- Be likely to complete the study as planned,
- Be considered appropriate candidates for participation in an investigative clinical trial with oral medication (e.g., no active substance abuse, acute major organ disease). It is of note that alcohol abuse would make these subjects more prone to develop TB-treatment–related liver-related toxicities.

Except for TB diagnosis laboratory test to determine eligibility that is to be performed locally, laboratory results from the central laboratory services provided by this study will be used to assess eligibility. Subjects not meeting all inclusion and exclusion criteria at the initial Screening visit may be rescreened **only once;** the subject will receive a new subject number. With the exception of a disqualifying viral genotype, a single repeat test (re-test) per analyte or assessment is allowed during the Screening Period to determine eligibility.

Subjects eligible for enrollment in this study must meet all of the following:

1. Subject or the subject's legal representative is willing and able to understand and provide signed and dated written informed consent prior to Screening;
2. Subject has plasma HIV-1 RNA ≥1000 copies/mL at Screening;
3. CD4+ cell count is ≥50 cells/mm^3 at Screening;
4. Subject is ≥18 years of age;
5. HIV-1-infected, ART-naïve; (≤10 days of prior therapy with any antiretroviral drug following a diagnosis of HIV-1 infection);
6. A female subject may be eligible to enter and participate in the study if she:

a. is of non-childbearing potential defined as either postmenopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy, or bilateral oophorectomy or,

b. is of childbearing potential, with a negative pregnancy test at both Screening and Day 1, and agrees to use one of the following methods of contraception to avoid pregnancy:

- Complete abstinence from intercourse from 2 weeks prior to administration of IP, throughout the study, and for at least 2 weeks after discontinuation of all study medications;
- Double-barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide);
- Approved hormonal contraception (see the SPM for a listing of examples of approved hormonal contraception) plus a barrier method while receiving RIF-containing TB treatment for subjects randomly assigned to the DTG arm, or approved hormonal contraception plus a barrier method for subjects randomly assigned to the EFV arm (regardless of RIF-containing TB treatment);
- Any intrauterine device (IUD) with published data showing that the expected failure rate is <1% per year (not all IUDs meet this criterion; see the SPM for an example listing of approved IUDs);
- Male partner sterilization prior to the female subject's entry into the study and this male is the sole partner for that subject;
- Any other method with published data showing that the expected failure rate is <1% per year.

Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of study drug. A childbearing potential female subject who starts the study using complete abstinence as her contraceptive method and decides to become sexually active must use the double barrier method either as a bridge to an approved hormonal contraception (if possible) or as a method of choice to be maintained from that moment onwards.

All subjects participating in the study should be counseled on safer sexual practices including the use of effective barrier methods (e.g. male condom/ spermicide).

7. New diagnosis of pulmonary, pleural, or LN tuberculosis based on identification of *Mycobacterium tuberculosis* using culture methods or GeneXpert (or other approved molecular test) on sputum or on samples collected by needle aspirate of pleural fluid or an affected LN;
8. RIF sensitivity of *Mycobacterium tuberculosis* either by culture or Gene Xpert (or other approved nucleic acid amplification test);
9. RIF-containing first-line TB treatment or an alternate RIF-containing TB treatment as described in Section 11.6 started up to a maximum of 8 weeks before randomization and no later than the screening date;
10. Karnofsky score ≥70% before randomization (see Section 11.7).

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

Exclusionary Medical Conditions

1. Any previous TB treatment (not including treatment for latent disease);
2. Evidence of RIF resistance of *Mycobacterium tuberculosis* either by culture or Gene Xpert (or other validated nucleic acid amplification test);
3. Expected requirement for TB treatment >9 months;
4. Concomitant disorders or conditions for which isoniazid, RIF, pyrazinamide, or ethambutol are contraindicated;
5. Central nervous system, miliary, or pericardial TB;
6. Women who are pregnant or breastfeeding;
7. Any evidence of an active AIDS-defining disease (CDC Category C; see Section 11.2). Exceptions include TB, cutaneous Kaposi's sarcoma not requiring systemic therapy, and historic CD4+ cell counts of <200 cells/mm^3;
8. Subjects with moderate to severe hepatic impairment (Class B or C) as determined by Child-Pugh classification (see Section 11.8); unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, or known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones);
9. Subjects positive for hepatitis B surface antigen (HBsAg) at screening;
10. Anticipated need for hepatitis C virus (HCV) therapy during the Randomized Phase of the study;
11. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class;
12. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the study medical monitor for inclusion of the subject;
13. Subjects who, in the investigator's judgment, pose a significant suicidality risk. Recent history of suicidal behavior and/or suicidal ideation may be considered as evidence of serious suicide risk.

Exclusionary Treatments Prior to Screening or Day 1

14. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening;

15. Treatment with any of the following agents within 28 days of Screening: radiation therapy, cytotoxic chemotherapeutic agents, any immunomodulators that alter immune response;
16. Treatment with any agent, other than licensed ART as allowed above (Section 4.2, inclusion criterion 5), with documented activity against HIV-1 in vitro/vivo within 28 days of first dose of the investigational product (IP);
17. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP;

Exclusionary Laboratory Values or Clinical Assessments at Screening

18. Any evidence of primary viral resistance to NRTIs, NNRTIs, or PIs based on the presence of any major resistance-associated mutation [IAS USA, 2013] in the Screening result or, if known, any historical resistance test result. Note: Retests of Screening genotypes are not allowed;
19. Any verified Grade 4 laboratory abnormality with the exception of Grade 4 triglycerides. A single repeat test is allowed during the Screening period to verify a result;
20. Any acute laboratory abnormality at Screening, which, in the opinion of the investigator, would preclude the subject's participation in the study of an investigational compound;
21. Alanine aminotransferase (ALT) ≥2 × upper limit of normal (ULN);
22. Hemoglobin ≤7.4 g/dL;
23. Platelet count <50,000/mm^3.

Notwithstanding these minimum inclusion and exclusion criteria, investigators must also follow country-specific guidelines where they exist when making decisions about subjects who are eligible for study participation.

4.4. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the IP, background NRTIs, and TB treatment.

4.5. Withdrawal Criteria

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. Withdrawn subjects will not be replaced.

Subjects permanently discontinuing study treatments prior to Week 52 are considered to be withdrawn from the study treatments and also from the study. Similarly, subjects in the DTG arm who enter the DTG OLE but permanently discontinue participation prior to commercial supplies of DTG becoming locally available (e.g., through public health services) are considered to be withdrawn from study treatment as well as from the study.

Subjects <u>may</u> be prematurely discontinued from the study for any of the following reasons:

- Subject or investigator non-compliance;
- At the request of the subject, investigator, or sponsor;
- The subject requires concurrent prohibited medications during the course of the study. However, the subject may remain in the study if in the opinion of the investigator and the medical monitor such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the subject.

Subjects <u>must</u> be prematurely discontinued from the study for any of the following reasons:

- Confirmed virologic withdrawal criteria as specified in Section 4.6.1.
- Subject requires changes (i.e., substitution or dose modification) of DTG or EFV. Permitted NRTI substitutions due to toxicity management are discussed in Section 5.1.5.
- Subject requires a TB treatment regimen that does not contain RIF.
- Subject requires interruption to RIF-containing regimens for longer than 14 days and is not on a bridging regimen. Permitted RIF-containing regimens are described in Section 11.6. Suitable bridging regimens are described in Section 6.4.3.1.1.
- Liver toxicity where stopping criteria specified in Section 6.4.3.1 are met and no compelling alternate cause is identified;
- Grade 4 clinical AE considered causally related to study drug or any component of TB treatment;
- Renal stopping criteria as described in Section 6.4.3.4 are met and no compelling alternate cause is identified;
- Hypersensitivity and rash criteria as described in Section 6.4.3.5 and Section 6.4.3.8, respectively are met and no compelling alternate cause is identified;
- Petechial rash due to RIF-induced thrombocytopenia as described in Section 6.4.3.9
- Pregnancy (intrauterine), regardless of termination status of pregnancy.

If a subject is withdrawn from the study, the protocol-defined assessments (if withdrawn at a routine study visit), the Withdrawal visit assessments, and if necessary the Follow-up visit assessments described in the Time and Events Table (Table 2) should be performed. All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any subject from the study. A Follow-up visit may occur approximately 4 weeks after the last dose of study treatment and is only required in subjects with ongoing serious AEs (SAEs) or non-serious laboratory or clinical AEs at the time of withdrawal.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (e.g., telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the electronic case report form (eCRF).

Subjects are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the Completion/Withdrawal section of the eCRF. Every effort should be made by the investigator to follow-up with subjects who withdraw from the study. In the event that a subject is prematurely discontinued from the study at any time due to an AE (see Section 6.4.4.1), the procedures stated in the Time and Events Table (Table 2) must be followed. Subjects who are withdrawn from the study will not be replaced.

Subjects may have a temporary interruption to their study treatment for management of toxicities.

4.6. Virologic Criteria for Subject Management and Viral Resistance Testing

Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 24 or beyond must have HIV-1 levels re-assessed using the algorithms in Figure 2 and Figure 3, which detail virologic criteria for **clinical management** of subjects who either require more careful monitoring (e.g., meet "**4-6 week plasma HIV-1 RNA testing criterion**") or have met a "**suspected or confirmed virologic withdrawal criterion.**" Investigators should not schedule re-assessment blood draws to take place in the presence of factors that could be associated with HIV-1 RNA levels ≥50 c/mL, such as intercurrent acute infection, treatment interruption due to toxicity management or non-compliance, or vaccination. Subjects should have received full doses of IP for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL.

If a subject meets the confirmed virologic withdrawal criteria, the plasma 'for storage sample' from the "suspected virologic withdrawal criterion" visit and the Day 1 sample will be used for HIV-1 genotype/phenotype testing. Subjects may continue to receive IP at the discretion of the investigator until results of resistance testing are available, at which time the subject must be discontinued from the study. If a subject is prematurely discontinued from the study, the investigator must make every effort to perform the evaluations outlined in the Time and Events Table (Section 6.1). These data will be recorded as they comprise essential evaluations needed to be done before discharging any subject from the study.

Note: Plasma samples with <400 c/mL of HIV-1 RNA will not be analyzed for viral resistance, as the protease/reverse transcriptase/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <400 c/mL.

Figure 2 Virologic Criteria for Subject Management at Week 24

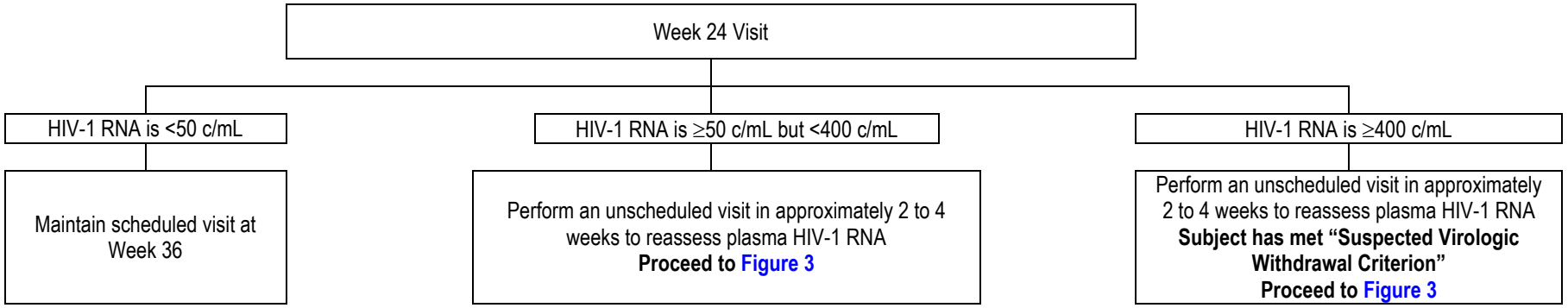
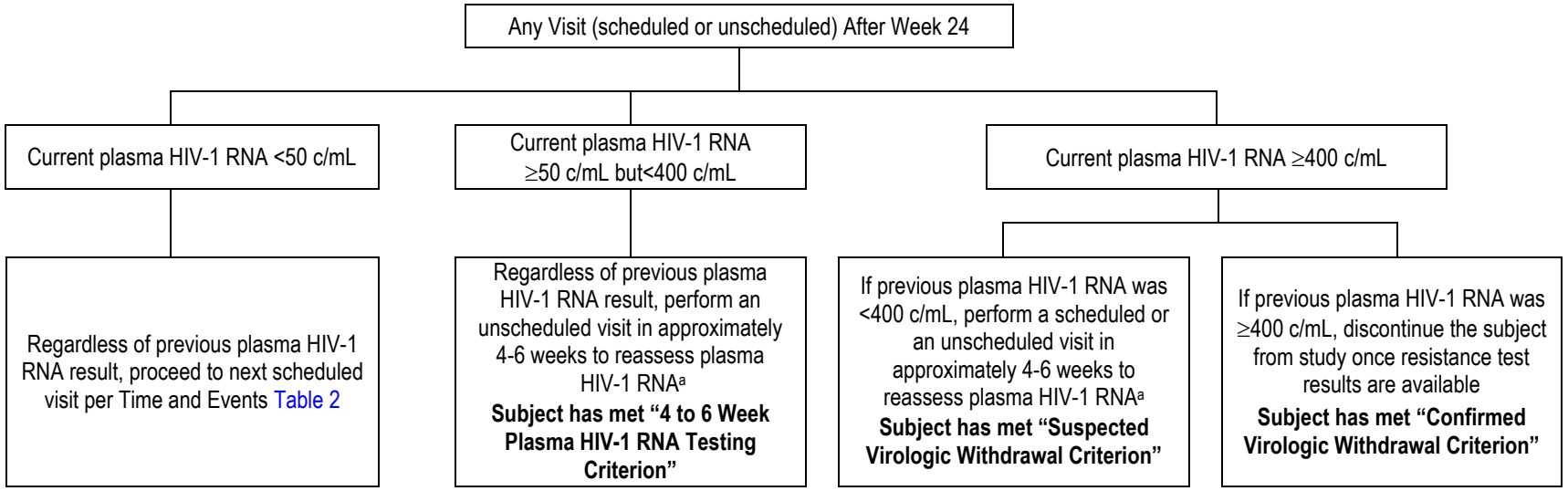


Figure 3 Virologic Criteria for Subject Management After Week 24



a. If current visit is the Week 48 scheduled visit then retest will occur at the Week 52 visit.

4.6.1. Management of Subjects Meeting Suspected Virologic Withdrawal Criteria

Only plasma HIV-1 RNA levels determined by the central laboratory (or a laboratory contracted by the central laboratory) will be used to assess virologic withdrawal criteria. Upon notification that a subject's plasma HIV-1 RNA level qualifies as meeting a suspected virologic withdrawal criterion, the investigator should query the subject regarding intercurrent illness, recent immunization, or interruption of therapy as inadequate adherence is a common cause of elevated HIV-1 RNA measurements.

All cases that meet a suspected virologic withdrawal criterion must be confirmed by a second measurement performed 4 to 6 weeks apart from the date of the original sample, unless one of the extenuating circumstances outlined below applies.

The following guidelines will be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the subject should receive full dose of all IP.
- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the subject should receive full dose of IP.
- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dose of IP.
- The subject should have received full doses of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

Sites should contact GSK to discuss individual subjects, whenever necessary.

At Week 48, repeat HIV-1 RNA testing is required for any HIV-1 RNA ≥50 c/mL and must be performed at the Week 52 study visit (Section 4.7).

4.7. Retest Criteria for Subjects With Plasma HIV-1 RNA Levels ≥ 50 c/mL at Week 48

Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 48 must have HIV-1 levels re-assessed by a second measurement performed at the Week 52 visit. Subjects should have received full doses of IP for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL.

Subjects with plasma HIV-1 RNA levels ≥400 c/mL should have a second measurement performed as outlined in Section 4.6.1.

4.8. Protocol-Defined Failure of TB Treatment

Tuberculosis treatment failure is defined by WHO [WHO 2010] as patients whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant strain at any point of time during the treatment, whether they are smear-negative or smear-positive.

Subjects with suspected TB treatment failure should be evaluated with a history, physical examination, sputum smear and culture with drug-susceptibility testing, and chest radiograph (TB treating physicians caring for the subject and local investigators should also use clinical judgment to determine if other evaluations are required) to determine whether they have clinically responded to therapy, even though their cultures have not converted or were not tested. The initial culture results and drug-resistance tests, treatment regimen, and adherence also should be reviewed. Samples from all available sites should be taken for repeat culture and drug-susceptibility testing, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or superinfection with a drug-resistant strain. If the results of repeat cultures and rapid resistance testing confirm, in consultation with an expert in the field, that the subject will require broadening of TB treatment by switching to a second-line TB treatment regimen without RIF then the subject must be withdrawn from the study.

4.9. Screening Failures

A subject is considered a screen failure if after providing informed consent, the subject's circumstances or conditions change or the outcome of a test or assessment becomes available which results in the subject's failure to meet one or more of the entry criteria, or results in the investigator deciding that the subject is no longer an appropriate study candidate.

Subjects who meet all entry criteria are randomized and assigned a randomization number. Subjects not meeting all inclusion and exclusion criteria at the initial screen may be rescreened **only once** and the subject will receive a new subject number at that time. With the exception of disqualifying viral genotype or TB culture or nucleic-acid–based RIF-susceptibility results indicating RIF resistance, a single repeat test (retest) per analyte or assessment is allowed during the Screening Period to determine eligibility. Subjects who are randomized into the study and subsequently withdrawn from the study for any reason may not be rescreened.

Except for results to confirm MTB which are analyzed locally, laboratory results from the central laboratory services provided by this study will be used to assess eligibility.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

Investigational product in this protocol refers to the investigational drugs DTG and the active control EFV. These will be supplied by GSK. For the purpose of this protocol, other ARTs administered in the study are not considered IP and will not be supplied by GSK. These will be sourced as local commercial material. Investigators will select a dual NRTI background for each subject. Tuberculosis drugs are also not considered IP and will be provided by the local TB program in accordance with national and local guidelines.

The contents of the label will be in accordance with all applicable regulatory requirements.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IP will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Adequate precautions must be taken to avoid direct contact with the investigational product which should be used in accordance with the manufacturer's instructions detailed in the prescribing information.

5.1.1. Tablet Formulation of DTG

DTG tablets are packaged as a full count of 30 film-coated tablets in a 45 cc high density polyethylene (HDPE) bottles with induction seal and child-resistant 33 mm closure. Tablets must be stored in the original package with the bottle tightly closed. The bottles contain a desiccant that must be kept in the bottle to protect tablets from moisture. The recommended storage conditions and expiry date where required, are stated on the product label.

Subjects must keep all IP in its original pack container. GSK will notify sites if and when data are available to support the use of pill boxes.

5.1.2. Tablet Formulation of EFV

EFV [Sustiva (efavirenz) US Product Information, 2013; Sustiva Summary of Product Information, 2014] is supplied as the EFV oral tablet, which contains 600 mg of EFV. EFV tablets, as manufactured by Bristol Myers Squibb, are yellow film-coated capsule-shaped tablets printed with "SUSTIVA" on both sides. Each pack/bottle will contain 30 film-coated tablets.

5.1.3. Background NRTIs

The investigator-selected dual NRTI background regimen must be determined and documented prior to randomization.

All background NRTIs are locally registered products. GSK will not reimburse or supply the investigator-selected background regimen unless required by the local regulatory authority or Institutional Review Board/Independent Ethics Committee (IRB/IEC) or unless previously agreed with study sites.

Those subjects for whom abacavir (ABC) is being considered as a component of the NRTI backbone should have been screened and be negative for the human leukocyte antigen (*HLA*)-*B*5701* allele before randomization takes place. This testing may be conducted as part of the study or may be performed by local laboratories. Results must be available for source document verification.

5.1.4. Dosage and Administration

	IP and background NRTI Dose and Dose Interval
Treatment Arm 1	
GSK1349572 (dolutegravir, DTG)	Twice-daily DTG 50 mg plus dual NRTI during TB treatment and for 2 weeks[a] following discontinuation of TB treatment, then once-daily DTG 50 mg with the same NRTI backbone through Week 52 and continued during the DTG OLE until DTG is locally approved and commercially available
Treatment Arm 2	
Efavirenz (EFV)	Once-daily EFV 600 mg plus dual NRTI through Week 52

Note: TB treatment including isoniazid, RIF, pyrazinamide, and ethambutol will be provided at standard doses by the NTP under program conditions.

a. Delays in switching from DTG twice daily to DTG once daily will not be considered an overdose.

DTG may be administered with or without food. EFV must be administered without food. For the dual NRTIs refer to the appropriate NRTI product information for treatment administration.

5.1.5. Protocol-Permitted Substitutions

A substitution of or switch between DTG or EFV is not allowed.

After consultation with the study medical monitor, switch of background NRTI therapy to an alternate approved NRTI therapy for toxicity or tolerability management is allowed one time. Switches of a background NRTI for any reason other than toxicity or tolerability management are not permitted in the study. The date of the decision to switch background NRTI for toxicity or tolerability management must be documented in the eCRF.

Note: Protocol-permitted substitutions (as described above), will not be coded as failures in this study regardless of the subject's HIV-1 RNA results at the time of the protocol-permitted substitution (Section 8.2.4).

Further information regarding alternate RIF-containing TB treatment regimens are described in Section 11.6.

5.2. Treatment Assignment

Informed consent must be obtained prior to any study procedures, including any screening assessment.

Subjects will be assigned to study treatment in accordance with the randomization schedule. Randomization will be conducted using a central randomization procedure following confirmation of fulfillment of study entry criteria. Subjects will be assigned (3:2 ratio to DTG or EFV-containing regimens, respectively) to study treatment in accordance with the computer-generated randomization schedule. The central randomization schedule will be generated by biostatistics using a validated SAS developed program. The stratification will be generated using an interactive voice response system (IVRS). Study site personnel will be required to contact the central randomization service for assignment of a unique identifier (designating the subject's randomization code) for each subject participating in the study. A unique treatment number will be assigned for each subject participating in the study.

Subjects who are randomly assigned into the study and subsequently withdrawn may not be rescreened.

5.3. Blinding

This will be an open-label study.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of study drug dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to PPD, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Treatment adherence will be evaluated using pill counts of unused study drug (DTG and EFV). This assessment will be conducted each time the subject receives a new (refill) supply of study drug through the Withdrawal visit or study completion. These data will be recorded in the subject's eCRF but will not be summarized for analysis purposes.

Data on start and end dates for TB treatment or ART including periods of interruptions (if applicable) will be documented.

5.6. Concomitant Medications and Non-Drug Therapies

Subjects should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential drug-drug interactions between such treatments and the study drugs. All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name and the dates of administration are to be recorded.

5.6.1. Permitted Medications and Non-Drug Therapies

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 5.6.2). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the subject and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn and only once scheduled visits are ≥4 weeks apart. This approach will minimize the risk of nonspecific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

Daily doses of RIF should be given at least 1 hour before the ingestion of antacids.

DTG should be administered 2 hours before or 6 hours after taking antacid products or sucralfate containing divalent cations (e.g., aluminum and magnesium) or calcium or iron supplements; alternatively, DTG can be taken together with calcium or iron supplement with a meal. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration of DTG with multivitamins is acceptable.

Metformin concentrations may be increased by DTG. Subjects taking DTG should be monitored for glucose control during therapy and a metformin dose adjustment may be required.

5.6.2. Prohibited Medications and Non-Drug Therapies

The following concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines (see Section 5.6.1 for guidance regarding non-HIV vaccines)
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy (see Exclusion Criteria, Section 4.3)
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited through the Randomized Phase (Day 1 to Week 48 plus a 4-week treatment extension) of the study. This includes topical agents with substantial systemic exposure and systemic effects. After the Randomized Phase (Day 1 to Week 48 plus a 4-week treatment extension), immunomodulators may be administered after discussion and agreement with the study medical monitor
- HCV therapy during the study is prohibited
- Chronic use of systemic (oral or parenteral) glucocorticoids should be avoided; however, short treatment courses of 30 days or less (e.g., for treatment of IRIS), replacement therapy (e.g., for Addison's Disease), and topical, inhaled, or intranasal use of glucocorticosteroid will be allowed

5.6.3. Prohibited Medications for Subjects Randomly Assigned to DTG

The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, the following medications must not be administered concurrently with DTG.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- St. John's wort (*Hypericum perforatum*)

Dofetilide and pilsicainide are prohibited as DTG may inhibit renal tubular secretion resulting in increased dofetilide/pilsicainide concentrations and potential for toxicity.

For prohibited medications related to TB therapy components, please refer to the local prescribing information for information on concurrent therapies.

For a detailed list of prohibited medications, please consult the SPM.

5.6.4. Prohibited Medications for Subjects Randomly Assigned to EFV

Efavirenz has the potential to impact the following drugs potentially requiring monitoring and dose adjustment:

- HMG-CoA reductase inhibitors are prohibited due to potential for decreased plasma concentrations; dosage should be individualized based on the goal of therapy and response.
- Methadone is prohibited due to potential for decreased plasma concentrations; subjects should be monitored for signs of withdrawal and methadone dose should be adjusted as appropriate
- Warfarin is prohibited because warfarin concentrations may be increased or decreased; international normalized ratio (INR) should be monitored and dosage should be adjusted as appropriate

5.7. Treatment After the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition whether or not ViiV/GSK is providing specific post-study treatment.

All subjects randomly assigned to receive DTG who have not prematurely discontinued from the study and who successfully complete 52 weeks of treatment will continue to have access to DTG (during the DTG OLE) until it is either locally approved and commercially available, the subject no longer derives clinical benefit, or the subject meets a protocol-defined reason for discontinuation. Investigative sites must make arrangements for provision of background NRTIs to all subjects to ensure continued

access to these medications during the DTG OLE (unless provision by the sponsor is mandated by local regulation).

Subjects randomized to the EFV arm will receive EFV through their Week 52 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access EFV and NRTIs (unless mandated by local regulation).

5.8. Treatment of Study Treatment Overdose

For this open-label study, any tablet intake exceeding the recommended daily number of tablets for study drug will be considered an overdose.

For the purposes of this study, an overdose is not an AE (refer to Section 6.4.4.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a serious AE (SAE) (see Section 6.4.4.2).

If an overdose occurs and is associated with an AE requiring action, all study drugs should be temporarily discontinued until the AE resolves. The investigator should use clinical judgment in treating overdose and also refer to the prescribing information for current ARTs, as ViiV/GSK is unable to recommend specific treatment.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Time and Events Schedule

Table 2 Time and Events Table

Procedures	Screening[a]	Randomized Phase									DTG Open-Label Extension[b]	Withdrawal	Follow-up[c]
		Week							4-week Treatment Extension	DTG Dose Switch (2 weeks post TB treatment completion)			
		Day 1	4	8	12	24	36	48	52	May occur any time after the 12 week visit	Week 60 and every 12 weeks thereafter		
Clinical and other assessments													
Written informed consent	X												
Subject demography	X												
Document pulmonary, pleural, or LN TB diagnosis[d]	X												
Document pre-TB treatment MTB culture result (e.g., sputum, LN, or pleural aspirate)[e]	X	X											
Document pre-TB treatment sputum smear results, if available	X												
Perform GeneXpert or equivalent and/or Document GeneXpert or equivalent RIF-sensitive MTB	X												

Procedures	**Screening[a]**	**Randomized Phase**									**DTG Open-Label Extension[b]**	**Withdrawal**	**Follow-up[c]**
		Week							**4-week Treatment Extension**	**DTG Dose Switch (2 weeks post TB treatment completion)**			
		Day 1	**4**	**8**	**12**	**24**	**36**	**48**	**52**	**May occur any time after the 12 week visit**	**Week 60 and every 12 weeks thereafter**		
Document the subject is on a RIF-containing first-line TB treatment and record TB regimen components	X[f]												
Record pre-specified TB regimen duration	X												
Documentation of TB regimen start date	X												
Inclusion/Exclusion criteria[f]	X	X											
Prior ART history	X												
Medical history[g]		X											
CDC HIV-1 classification	X	X											
Physical examination[h]	X	X	X	X	X	X	X	X	X		X	X	X
Body weight and height		X											
Current medical conditions		X											
Cardiovascular risk assessment[i]		X											
Concomitant medication	X	X	X	X	X	X	X	X	X		X	X	X
HIV associated conditions			X	X	X	X	X	X	X		X	X	
Columbia Suicidality Severity Rating Scale[j]		X[j]	X	X	X	X	X	X	X		X	X	
Adverse events		X	X	X	X	X	X	X	X		X	X	X
SAEs	X[k]	X	X	X	X	X	X	X	X		X	X	X

Procedures	**Screening[a]**	**Randomized Phase**									**DTG Open-Label Extension[b]**	**Withdrawal**	**Follow-up[c]**
		Week							**4-week Treatment Extension**	**DTG Dose Switch (2 weeks post TB treatment completion)**			
		Day 1	**4**	**8**	**12**	**24**	**36**	**48**	**52**	**May occur any time after the 12 week visit**	**Week 60 and every 12 weeks thereafter**		
TB-associated IRIS assessment[l]			X	X	X								
Laboratory assessments													
Quantitative plasma HIV-1 RNA PCR	X	X	X	X	X	X	X	X	X[m]		X	X	
Lymphocyte subsets	X	X	X	X	X	X	X	X	X		X	X	
Plasma for storage[n]	X	X	X	X	X	X	X	X	X		X	X	
Plasma for HIV genotyping	X												
HLA-B 5701* testing[o]	X												
Clinical chemistry	X	X	X	X	X	X	X	X	X		X	X	X
Hematology	X	X	X	X	X	X	X	X	X		X	X	X
PT/INR	X												
Fasting lipids and glucose[p]		X				X		X					
Pregnancy test[q]	S	U	S	S	S	S	S	S	S		S	S	
HBsAg and hepatitis C (anti-HCV Ab)	X												
Pharmacogenetic sample[r]		X											
Pharmacokinetic plasma sample[s]				X		X	X	X					
Dispense PK dosing diary card			X		X	X	X			X[t]			

Procedures	Screening[a]	Randomized Phase									DTG Open-Label Extension[b]	Withdrawal	Follow-up[c]
		Week							4-week Treatment Extension	DTG Dose Switch (2 weeks post TB treatment completion)			
		Day 1	4	8	12	24	36	48	52	May occur any time after the 12 week visit	Week 60 and every 12 weeks thereafter		
Investigational product													
IVRS	X	X	X	X	X	X	X	X	X	X[u]	X	X	X
Dispense IP		X	X	X	X	X	X	X	X[v]	X	X[v]		
IP accountability (pill counts)			X	X	X	X	X	X	X	X	X	X	

ART = antiretroviral therapy; CDC = Centers for Disease Control; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus-1; HLA-B = human leukocyte antigen-B; INR = international normalized ratio; IP = investigational product; IVRS = interactive voice response system; LN = lymph node; MTB = *Mycobacterium tuberculosis*; PCR = polymerase chain reaction; PT = prothrombin time; RIF = rifampicin; RNA = ribonucleic acid; SAE = serious adverse event; TB = tuberculosis

a. The 14-day Screening Period may be extended to 28 days. Randomization may occur as soon as all Screening results are available and up to 8 weeks after TB treatment initiation
b. Subjects randomly assigned to the DTG arm and complete the Randomized Phase through the Week 52 visit will enter into the DTG OLE. Subjects completing the DTG OLE must return to the clinic when transitioning to commercial supplies for an end of OLE visit. Study assessments will be conducted as specified for the withdrawal visit.
c. A Follow-up visit will be conducted 4 weeks after the last dose of study provided IP and is required only if a subject has ongoing AEs or laboratory abnormalities at the last on-study visit. The assessments performed should reflect what is considered medically necessary to assess the event(s).
d. Smear positive or culture positive, including sample source recorded in eCRF.
e. Results may be documented any time between Screening and Day 1.
f. Inclusion/exclusion criteria will be fully assessed at the Screening visit (to include Karnofsky assessment). Changes between the screening visit and the Day 1 visit should be assessed to ensure eligibility, including additional assessments performed at Day 1.
g. Full medical history will be collected. Targeted medical history assessments will include cardiovascular, gastrointestinal (e.g., GI bleeding, PUD), metabolic (e.g., Type I or II DM), psychiatric (e.g. depression), renal (e.g. nephrolithiasis, nephropathy, renal failure) and neurological disorders.
h. Limited physical examination to include blood pressure at Baseline (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
i. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease.
j. The Columbia-Suicidality Severity Rating Scale (subject completed questionnaire) is to be administered if a validated version in the appropriate language is available for the subject. The assessment will be performed only in countries where the validated questionnaire exists in the appropriate language. On Day 1, the questionnaire should be

completed prior to randomization.

k. Only SAEs related to study participation or to a concomitantly administered GSK/ViiV product will be collected between obtaining informed consent and administration of IP at Day 1.
l. TB-associated IRIS criteria are described in Section 6.4.6; if any of the major and/or minor criteria are identified they will be captured and reported as AEs. Toxicity management related to TB-associated IRIS cases are described in Section 6.4.3.3.
m. Quantitative plasma HIV-1 RNA are **ONLY** for subjects who had HIV-1 RNA >50 c/mL at the Week 48 visit.
n. Plasma samples for storage will be collected at each visit for possible future analyses (including but not limited to HIV-1 RNA genotypic and phenotypic analyses, HIV-1 RNA levels, and immunological parameters). These samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable. Plasma for storage sample should also be collected at the unscheduled visit for retesting suspected virologic withdrawal. Additionally, for genotypic and phenotypic resistance analyses baseline samples from all subjects will be used and later samples in cases of confirmed virologic withdrawal criteria met (for paired baseline and endpoint genotypes).
o. Subjects starting ABC as one of the NRTIs must have been screened and be negative for the *HLA-B*5701* allele.
p. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
q. Pregnancy testing will be conducted (women of childbearing potential only) on serum samples with the exception of Day 1, which must be a urine test to confirm status prior to administration of IP.
r. Informed consent for optional pharmacogenetics (PGx) research must be obtained before collecting a sample. Collection of the PGx sample at Day 1 is preferred; however, this sample may be collected at any time during the study.
s. For subjects randomly assigned to EFV, mid-dosing interval samples will be collected at Weeks 8, 24, 36, and 48. For subjects randomly assigned to DTG, 1 sample each for pre-dose, 1 to 3 hours post-dose, 4 to 12 hours post-dose will be collected at Weeks 8 and 36, and 1 sample pre-dose will be collected at Weeks 24 and 48. If PK sampling is not performed the visit will be rescheduled to collect the PK sample and if applicable the subject will be provided a new diary card. Instructions on PK sample collection are described in Section 6.5.2. Blood samples should be collected into K2EDTA tubes.
t. Collect DTG twice daily PK diary card and provide the subject with the DTG once daily PK diary card.
u. The IVRS will capture the point at which the subject is within 2 weeks of completing their TB treatment and the site will notify the subject to return to the clinic for the DTG switch visit in order to dispense the DTG 50 mg once daily dose.
v. For subjects receiving DTG during the DTG OLE only.

6.1.1. TB Time and Events Schedule

Table 3 TB Time and Events Table

Procedures	TB Treatment Intensive Phase		TB Treatment Continuation Phase		
	Baseline	Month 2	Month 4	Month 6	Month 9
Laboratory assessments					
Collection of sputum samples for MTB smear and culture testing[a]	X	X	X	X	X
TB regimen assessments					
TB medications[b]	X	X	X	X	X
TB treatment interruptions[c]		X	X	X	X
TB treatment re-introduction[d]		X	X	X	X
Document RIF-sensitivity[e]	X	X	X	X	X

MTB = *Mycobacterium tuberculosis*, TB = tuberculosis

a. To be performed at the local laboratory. The laboratory and method for that subject should remain the same throughout the study. Results of testing will be recorded in the eCRF. Sputum does not need to be collected from subjects with pleural or lymph node TB who do not also have pulmonary TB. If subjects are no longer producing sputum at 4 months, 6 months, and 9 months and no sputum sample can therefore be collected, then this fact must be recorded in the eCRF. Subjects who complete their TB treatment at 6 months, do not require a sputum sample to be collected at 9 months, unless clinically indicated (investigator decision).
b. Record all TB treatment medications taken during the intensive and continuation phases on the TB treatment medication eCRF.
c. Any missed doses or changes to the regimen should be recorded on the TB treatment medication eCRF. If the TB regimen is interrupted for more than 14 days, the subject must be withdrawn from the study.
d. Re-introduction guidelines are described in Section 6.4.3.1.1.
e. Rifampicin susceptibility testing at baseline is mandatory. The investigator may repeat RIF susceptibility testing at other times, as clinically indicated. If at any time, an isolate is found to be RIF-resistant, then the subject must be withdrawn from the study.

6.2. Critical Baseline Assessments

Written informed consent must be obtained from each potentially eligible subject (or his/her legal representative) by study site personnel prior to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the IRB/IEC. After signing an informed consent, subjects will complete Screening assessments to determine subject eligibility. Each subject being screened for study enrollment evaluation will be assigned a subject number at the Screening visit. This number will be given sequentially in chronological order of subject presentation according to a numeric roster provided by PPD.

6.2.1. Screening Assessments

Assessments to be conducted at Screening are provided in the Time and Events schedule (Table 2).

All subjects will complete the Screening Period approximately 14 days prior to Baseline (Day 1) during which time all clinical and laboratory assessments of eligibility must be performed and reviewed. The Screening Period may be extended to 28 days to

accommodate availability of all Screening assessment results and scheduling. All Screening results must be available prior to randomization.

Eligibility criteria must be carefully assessed at the Screening visit. Physical examinations should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Smear-positive sample, site from which sample was obtained (e.g., sputum, LN, or pleural aspirate) and sputum smear grade result, culture date of collection and result (if available), results of Gene Xpert test, including RIF genotypic susceptibility testing will be recorded at the Screening visit.

Subjects who meet all entry criteria are randomly assigned to treatment and assigned a randomization number. Subjects not meeting all inclusion and exclusion criteria at the initial screen may be rescreened **only once** and the subject will receive a new subject number at that time. With the exception of a disqualifying viral genotype or documentation of RIF resistance, a single repeat test (re-test) per analyte or assessment is allowed during the Screening Period to determine eligibility. Subjects who are randomized into the study and subsequently withdrawn from the study for any reason may not be rescreened.

Note: Where *HLA-B*5701* screening is considered standard of care, it is recommended that investigators screen for presence of the *HLA-B*5701* allele in any subject for whom an ABC-containing product (e.g., ZIAGEN™, EPZICOM™, KIVEXA™) may be considered as part of background regimen and *HLA-B*5701* status is unknown (even if the subject has previously tolerated ABC). **Use of ABC in subjects known to carry *HLA-B*5701* is not recommended** and should be considered only under exceptional circumstances where potential benefit outweighs the risk and only under close medical supervision.

6.2.2. Baseline Assessments (Day 1)

Assessments to be conducted at Baseline (Day 1) are provided in the Time and Events schedule (Table 2).

At Day 1 and prior to randomization, any changes to the eligibility parameters must be assessed and any results required prior to randomization (e.g., Day 1 urine pregnancy test for women of childbearing potential) must be available and reviewed.

Cardiovascular risk factors will be assessed at Baseline and assessments will include smoking status and history and family history of cardiac events.

For subjects who agree to the optional assessment, a whole blood sample for pharmacogenetic (PGx) research should be collected at Day 1; however this sample may be collected at any time during the study (see Section 11.1).

6.3. Efficacy

6.3.1. Efficacy Evaluations

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events Table (Table 2). Methods to be used may include but are not limited to the Abbott Realtime HIV-1 Assay with lower limit of detection (LLOD) 40 c/mL. In some cases (e.g., where the HIV-1 RNA is below the LLOD for a given assay) additional exploratory methods may be used to further characterize plasma HIV-1 RNA levels.

Lymphocyte Subsets

Blood samples will be collected for assessment of lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ lymphocyte counts) according to the Time and Events Table (Table 2).

Sputum MTB Cultures

Sputum samples will be collected for assessment of positive TB cultures according to the TB Time and Events Table (Table 3). TB cultures are to be performed locally and results will be collected in the eCRF.

CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the Time and Events Table (Table 2). HIV associated conditions will be assessed according to the 1993 CDC Revised Classification System for HIV Infection in Adults (see Section 11.2). Indicators of clinical disease progression are defined as:

CDC Category A at enrollment→ Category B event;

CDC Category A at enrollment→ Category C event;

CDC Category B at enrollment→ Category C event;

CDC Category C at enrollment→ New Category C Event;

CDC Category A, B or C at enrollment→ Death

6.3.2. Primary Efficacy Endpoint

The primary endpoint will be the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population in the DTG arm. This endpoint will also be evaluated in the modified ITT-E (MITT-E) population.

6.3.3. Secondary Efficacy Endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the EFV arm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related AE, safety stopping criteria, or lack of efficacy);
- Changes from baseline in CD4+ counts at Week 24 and Week 48.

6.3.4. Tertiary Efficacy Endpoints

- Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses and death);
- Proportion of subjects with TB treatment success (using the WHO definition, to be detailed in the reporting and analysis plan [RAP]);
- Proportion of subjects with pulmonary MTB who are sputum culture-negative 2 months after starting TB treatment.

6.4. Safety

Safety assessments will be conducted according to the Time and Events Table (Table 2) and will include the following:

- Monitoring and recording all AEs and SAEs. Additional information on the time period and frequency of detecting AEs and SAEs is provided in Section 6.4.12;
- Regular monitoring of hematology and blood chemistry parameters;
- Periodic assessment of fasting lipids and glucose;
- Physical examinations should be conducted as part of normal routine clinical care but will not be entered systematically in the eCRF. Abnormalities noted during any examination must be recorded in the eCRF (e.g., in the current medical conditions or AE logs);
- Evaluation and documentation of all concomitant medications and blood products received;
- Suicidality monitoring using the Columbia-Suicide Severity Rating Scale (C-SSRS; Section 6.4.10).

Any appropriately qualified site personnel (e.g., investigator, sub-investigator, or study coordinator/nurse) can perform assessments. With the exception of TB culture, a central laboratory chosen by GSK/ViiV will undertake all routine scheduled laboratory evaluations within the study. Refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipping for each laboratory test.

Table 4 Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[b]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine[c]
PT/INR[d]			
Fasting Lipid Panel[e]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			
Plasma HIV-1 RNA			
CD4+ cell counts			
Hepatitis B (HBsAg) and hepatitis C (anti-HCV Ab)[d]			
Pregnancy test for women of childbearing potential[f]			
*HLA-B*5701* screening[d]			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

a. Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b. Fasting glucose will be collected at Day 1 and Weeks, 24, and 48 during the study. For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
c. Glomerular filtration rate (GFR) will be estimated by the central laboratory using the CKD-EPI formula using serum creatinine [Inker, 2012].
d. Screening visit only
e. For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
f. Urine pregnancy test and serum pregnancy test will be performed according to Table 2.

6.4.1. Safety Endpoints

- Incidence and severity of all AEs, SAEs, and laboratory abnormalities;
- Proportion of subjects who permanently discontinue IP or TB treatment due to AEs or death;
- Proportion of subjects who temporarily discontinue IP and/or TB therapy due to AEs;
- Proportion of subjects with TB-associated IRIS

  Note: the clinical team will review the AE terms and HIV conditions in order to identify TB-associated IRIS cases. TB-associated IRIS criteria are described in Section 6.4.6 and toxicity management for TB-associated IRIS cases are described in Section 6.4.3.3.

6.4.2. Toxicity Management

Adverse events that occur during the study should be evaluated by the investigator and graded according to the Division of AIDS (DAIDS) toxicity scales (see Section 11.3). Additional information regarding detecting, documenting, and reporting AEs and SAEs are available in Section 6.4.3.9.

Investigational product may be interrupted at the discretion of the investigator and according to the severity of the AE. If one or more antiretroviral drugs are held due to toxicity or AEs, generally, all antiretroviral drugs should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each antiretroviral drug of the regimen. In some cases (e.g., EFV), short continuation of the dual NRTI components of the regimen after interruption of the third antiretroviral drug may be appropriate in order to minimize the risk of development of resistance.

No toxicity-related dose reductions of IP will be allowed. Investigational product should be restarted as soon as medically appropriate; in general, this should be no longer than 4 weeks after interruption (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of IP or temporary interruption of one or more but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Guidance is provided below on subject management and IP interruptions based on the severity of the AE; for specific toxicities, please refer to Section 6.4.3. All changes in IP must be accurately recorded in the subject's eCRF.

When possible, concomitant medications (like TB treatment components) should be held first at the discretion of the principal investigator if he/she suspects they are contributing to the toxicity

Toxicities That the Investigator Considers Related or Possibly Related to TB Treatment

Toxicities that the investigator considers related or possibly related to TB treatment should be managed with reference to applicable product labeling and local guidelines.

Note: In instances where both IP and TB treatments are interrupted due to either a clinical or laboratory toxicity, and it is decided to re-introduce these agents e.g., upon event improvement or resolution (following consultation with the medical monitor for Grade 3 toxicities), the TB treatment should be restarted first according to Section 11.6, followed by trimethoprim-sulfamethoxazole (TMP-SMX), and then ART.

Toxicities That the Investigator Considers Related or Possibly Related to one or More NRTIs

Toxicities that the investigator considers related or possibly related to one of the background NRTIs may be addressed by substitution of the medication for another approved NRTI one time during the study (Section 5.1.5). In addition, toxicities that the

investigator considers related or possibly related to any NRTI should be managed with reference to applicable product labeling.

Note: For subjects receiving an ABC-containing product as part of the background regimen, in the event of a discontinuation of ABC for any reason, reinitiation of this drug should be undertaken with caution. The investigator should obtain a complete history of the events surrounding the discontinuation of the ABC-containing product, evaluate for the possibility of a clinically suspected hypersensitivity reaction (HSR), and initiate subject management as outlined in the local country prescribing information, regardless of a subject's *HLA-B*5701* status. Screening for the presence of *HLA-B*5701* is recommended prior to reinitiating treatment with ABC-containing products in subjects of unknown *HLA-B*5701* status who have previously tolerated ABC.

Grade 1 or Grade 2 Toxicity/Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE or toxicity may continue IP at the discretion of the investigator. For exceptions to this guideline see Section 6.4.3.

Subjects who voluntarily decide to terminate their participation in the study due to a Grade 1 or 2 AE should complete the Withdrawal and Follow-up visit.

Grade 3 Toxicity/Adverse Event

Subjects who develop a Grade 3 AE or Grade 3 toxicity should be managed as follows:

If the investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by IP, dosing may continue after discussion with the medical monitor.

Subjects who develop a Grade 3 AE or toxicity that the investigator considers related or possibly related to the IP should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, IP may be restarted.

Should the same Grade 3 AE recur within 28 days in the same subject, the IP should be permanently discontinued and the subject withdrawn from study. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to complete the Withdrawal visit. A Follow-up visit should be performed 4 weeks after the last dose of IP.

Subjects with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug-related causes, and, following discussion with the medical monitor, may continue IP if the investigator has compelling evidence that the toxicity is not related to IP.

Exceptions are noted for lipid abnormalities in Section 6.4.3.6.

Grade 4 Toxicity/Adverse Event

Subjects who develop a Grade 4 AE or toxicity should have IP permanently discontinued. However, if the investigator has compelling evidence that the AE is not causally related to the IP, dosing may continue after discussion with and assent from the medical monitor. Subjects should be rechecked each week until the AE returns to Grade 2.

Subjects experiencing Grade 4 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and are encouraged to complete the Withdrawal and Follow-up visit as noted above.

Subjects with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue therapy if the investigator has compelling evidence that the toxicity is not related to IP. Exceptions are noted for lipid abnormalities in Section 6.4.3.6. A Follow-up visit should be performed 4 weeks after the last dose of IP if AEs or laboratory abnormalities are ongoing.

6.4.3. Specific Toxicity Management

General guidelines are described below for the management of specific toxicities that are considered to be related or possibly related to IP, background NRTIs, and TB treatment and include the following:

- Liver chemistry stopping and follow-up criteria (Section 6.4.3.1)
- IRIS (Section 6.4.3.3)
- Decline in renal function (Section 6.4.3.4)
- Allergic reaction (Section 6.4.3.5)
- Hypertriglyceridemia/hypercholesterolemia (Section 6.4.3.6)
- Creatine phosphokinase (CPK) elevation (Section 6.4.3.7)
- Rash (Section 6.4.3.8)
- Petechial rash due to RIF-induced thrombocytopenia (Section 6.4.3.9)

Subjects who permanently discontinue IP for reasons of toxicity should be followed weekly until resolution or stabilization of the AE and encouraged to complete the withdrawal and Follow-Up study evaluations as noted above.

6.4.3.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of IP and the Follow-up period. If ALT >2 × ULN, liver chemistries should be monitored weekly for 2 weeks, then every 2 weeks thereafter until normalized.

While receiving IP co-administered with TB treatment, both will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin; bilirubin fractionation required)
    - NOTE: Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event meets liver stopping criteria;
- ALT ≥3 × ULN with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR
- ALT ≥5 × ULN; regardless of symptoms

After completion of TB treatment, while receiving IP, ART will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin; bilirubin fractionation required)
    - NOTE: Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event meets liver stopping criteria;
- ALT ≥3 × ULN (if baseline ALT is <ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR
- ALT ≥3 × baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥ 5 × ULN and <8 × ULN (after TB treatment is complete) that persists ≥2 weeks (with bilirubin <2 × ULN and no signs or symptoms of acute hepatitis or hypersensitivity); ALT ≥5 × ULN but <8 × ULN (after TB treatment is complete) and cannot be monitored weekly for >2 weeks; and subjects who develop ALT ≥5 × ULN should be followed weekly until resolution or stabilization (ALT <5 × ULN on 2 consecutive evaluations);
- ALT > 8 × ULN; regardless of symptoms.

When liver chemistry stopping criteria are met, do the following:

- Immediately hold IP;
- According to guidelines, isoniazid, pyrazinamide, RIF, and TMP-SMX should be stopped simultaneously (when applicable) with the interruption of the ART;
- Report the event to the medical monitor within 24 hours of learning its occurrence (see Table 7 and Section 6.4.14);

- Complete the liver event and SAE eCRFs, where applicable, (see Section 6.4.14);
- Complete the liver imaging, liver biopsy, or both eCRFs if these tests are performed;
- Perform liver event follow-up assessments (described in this section), and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below;
- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow-up assessments (described in this section), and close monitoring;
- A specialist or hepatology consultation is recommended;
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase, and bilirubin) resolve, stabilize, or return to within baseline values;

Make every attempt to carry out the liver event follow-up assessments described below:

- Viral hepatitis serology including:
- Hepatitis A IgM antibody;
- HBsAg and hepatitis B core antibody (IgM);
- Hepatitis C RNA;
- Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Blood sample for PK analysis, obtained within 60 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of IP prior to blood draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM;
- Serum acetaminophen test (APAP adduct test). Please refer to the SPM and Quest Diagnostics Laboratory manual for further details;
- Serum CPK and lactate dehydrogenase;
- Fractionate bilirubin, if total bilirubin is ≥1.5 × ULN;
- Obtain complete blood count with differential to assess eosinophilia;
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;

- Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form. Record alcohol use on the liver event alcohol intake case report form.

6.4.3.1.1. Alternate RIF-Containing TB Treatment Regimen and Bridging Regimen

In cases of TB treatment interruption due to hepatotoxicity, until the cause of the hepatotoxicity is identified it may be necessary to treat the subject's tuberculosis with a bridging non-RIF–containing anti-tuberculosis regimen with low risk of hepatotoxicity. Drugs that may be used include (i) ethambutol, (ii) an injectable: e.g., aminoglycoside (such as streptomycin, amikacin, and kanamycin) or capreomycin or (iii) a fluoroquinolone (e.g., moxifloxacin or levofloxacin). A bridging regimen should be used to avoid reaching the 14-day treatment interruption limit and therefore avoid having to withdraw a study subject from the study.

Both CDC and BHIVA guidelines recommend that patients be treated with two or more active drugs drawn from each of the groups listed (i) to (iii) above (i.e., ethambutol and streptomycin, or ethambutol and moxifloxacin) while waiting for standard therapy to be reintroduced in consultation with a local expert. A note for caution comes from reports of severe hepatotoxicity with moxifloxacin.

Tuberculosis treatment may be re-introduced when ALT <2 × ULN. Suggested re-introduction regimen schedules after TB treatment interruption are provided in Table 5 and Table 6, which describe options excluding ethambutol (12) or isoniazid (13) for testing re-exposure to TB drugs, respectively. TB treatment should be restarted first [BHIVA Guidelines, 2011], followed by TMP-SMX, if required for patient care, followed by ART. Daily monitoring of the patient's condition and liver chemistries (ALT, AST, total bilirubin, alkaline phosphatase) is required during the reintroduction. Guidance from a local expert should be sought.

The time on the standard regimen (i.e., the initial WHO first-line TB regimen) should count towards time on the acceptable alternate RIF-containing TB treatment, provided the treatment interruption was no longer than 14 days [CDC 2003 Guidelines]. Only time on full-dose of the WHO first-line regimen or listed in Section 11.6 counts towards time on a TB regimen. Time on partial doses of TB drugs as part of the reintroduction does not count, but time on the bridging regimen does count. Further information on alternate RIF-containing TB treatment regimens are described in Section 11.6.

Table 5 Re-Introduction Guidelines for Regimen 1

Day	Rifampicin	Isoniazid	Pyrazinamide
1		50 mg	
2		150 mg	

Day	Rifampicin	Isoniazid	Pyrazinamide
3		full dose	
4	75 mg	full dose	
5	150 mg	full dose	
6	300 mg	full dose	
7	full dose	full dose	
8	full dose	full dose	250 mg
9	full dose	full dose	500 mg
10	full dose	full dose	1 g
11	full dose	full dose	full dose
12	full dose	full dose	full dose
13	full dose	full dose	full dose

kg = kilogram; mg = milligram; g = gram

Table 6 Re-Introduction Guidelines for Regimen 2

Day	Rifampicin	Ethambutol	Pyrazinamide
1	75 mg		
2	150 mg		
3	300 mg		
4	450 mg <50 kg or 600 mg >50 kg		
5	450 mg/600 mg	5 mg/kg	
6	450 mg/600 mg	10 mg/kg	
7	450 mg/600 mg	15 mg/kg	
8	450 mg/600 mg	15 mg/kg	250 mg
9	450 mg/600 mg	15 mg/kg	500 mg
10	450 mg/600 mg	15 mg/kg	1 g
11	450 mg/600 mg	15 mg/kg	1.5 g <50 kg or 2 g >50 kg
12	450 mg/600 mg	15 mg/kg	1.5 g/2 g

kg = kilogram; mg = milligram; g = gram

6.4.3.2. Restarting Investigational Product

Drug restart/rechallenge following liver events that are possibly related to IP

Liver toxicity in the setting of concomitant TB treatment and ART is most commonly related to the antituberculosis medications rather than the HIV medications. As described above, TB treatment (isoniazid, RIF, and pyrazinamide) should all be discontinued (Section 11.6 for alternate TB therapy recommendations), along with all antiretrovirals and TMP-SMX, if being administered, when liver stopping criteria are met. In some cases (e.g., EFV), short continuation of the dual NRTI components of the regimen after interruption of the third antiretroviral drug may be appropriate in order to minimize the risk of development of resistance. Liver chemistries should be followed at least twice weekly until they have returned to <2 × ULN. Re-introduction of TB treatment should then be undertaken first as described in Section 11.6, followed by TMP-SMX, and then ART should be restarted.

If liver toxicity is due to TB treatment and an alternative anti-TB treatment containing RIF can be successfully introduced, the authorization for restarting the IP may be discussed between the investigator and the study medical monitor, without the need for

approval from the ViiV Safety and Labeling Committee (VSLC) (see details in Section 11.5). If liver toxicity is not due to TB treatment, the case will need VSLC approval to restart DTG (this approval can be ad hoc).

For Grade 4 ALT elevations (≥10 × ULN) it is recommended that the subject not be rechallenged with pyrazinamide. Alternate RIF-containing TB treatment regimens are described in Section 11.6 [BHIVA Guidelines Section 7.2, 2011 and CDC 2003 Section 8.8.2].

The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.

Subjects approved by ViiV/GSK for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for 1 month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol.

Refer to Section 11.5 for further details.

Drug restart following transient resolving liver events not related to IP

Refer to Section 11.5 for further details.

6.4.3.3. TB-Associated IRIS Toxicity Management

Subjects presenting with Grade 3 (except Grade 3 TB-associated IRIS toxicity manifested only by respiratory signs and symptoms) and Grade 4 TB-associated IRIS toxicity should have the IP withheld and be rechecked each week until the AE returns to Grade ≤2. Once the AE is Grade ≤2, IP may be restarted.

Grade 3 TB-associated IRIS toxicity restricted to respiratory signs and symptoms may be managed by the investigator including, but not limited to, assessment of treatment failure and therapy with steroids, for a period of 1 week without having the IP withheld. After this period, if the event persists as a Grade 3 event, withholding the IP and having weekly follow-ups until the AE returns to Grade ≤2 would be required.

6.4.3.4. Decline in Renal Function

Subjects who experience an increase in creatinine from Baseline of 45 µMol/L (or 0.5 mg/dL) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine ratio should be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

Subjects who have a decline in estimated GFR (using the CKD-EPI method) of >50% must return for a confirmatory creatinine assessment as soon as possible. A urinalysis and urine albumin/creatinine ratio should be done at this confirmatory visit. If the estimated GFR has declined by >50% (confirmed), then IP should be withheld and the investigator should contact the study medical monitor to discuss the rationale for restarting IP (if

appropriate). Consideration for confounding factors (e.g., other medications, dehydration, concurrent medications) should be taken into account and a nephrology consult may be obtained. If a subject is also receiving TDF, then a switch to an alternate NRTI should be considered if restarting IP. One background NRTI change is allowed for management of drug toxicity as described in Section 5.1.5. If IP is not reinitiated the subject must be withdrawn.

6.4.3.5. Allergic Reaction

Grade 1 or 2: Subjects may continue IP at the discretion of the investigator. The subject should be advised to contact the investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Grade ≥3: Subjects with allergic reactions that are considered to be possibly or probably related to the IP should permanently discontinue the IP regimen and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

Allergic reactions that the investigator considers related or possibly related to TB treatment should be managed with reference to applicable product labeling, local guidelines and, where the re-introduction of TB treatment is applicable, the recommendations outlined in Section 11.6.

Subjects receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information.

6.4.3.6. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Time and Events Table (Table 2). Subjects who experience asymptomatic triglyceride or cholesterol elevations may continue to receive IP.

6.4.3.7. Creatine Phosphokinase Elevation

Grade ≥3: Subjects with an elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment.

Grade 4: Subjects with an elevation in CPK should have a repeat assessment after the subject has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the IP, IP should be discontinued and the subject withdrawn from the study.

A history regarding use of drugs known to cause an increase in CPK (such as statins) and physical activity or exercise preceding the CPK evaluation should be obtained.

6.4.3.8. Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first 10 weeks of treatment, rarely require

interruptions or discontinuations of therapy and tend to resolve within 2 to 3 weeks. No instances of serious skin reaction, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, have been reported for DTG in clinical trials. Additional information on characterization of HSR and rash observed with DTG-containing ART is in the current version of the IB [GlaxoSmithKline Document Number RM2007/00683/07]. Approximately one-fourth of adult subjects treated with EFV in clinical studies presented rash of any grade, with rare cases (<1%) being Grade 3 or higher. For information on rashes observed in EFV treated subjects refer to EFV product information [Sustiva (efavirenz) US Product Information, May 2013; Sustiva Package Insert, 2013; Sustiva Summary of Product Information, 2014].

TB treatment regimens commonly cause rashes that are typically mild/moderate in severity and usually start within the first 2 months of treatment initiation. Mild rashes without mucosal involvement can be treated symptomatically. More widespread worsening rashes or those with systemic symptoms require all drug cessation. It is recommended that when TB drugs, HIV drugs, and TMP-SMX are interrupted concomitantly due to treatment emerging rash that TB drugs be reintroduced first, then TMP-SMX, and finally the ART, in a similar regimen as the one suggested for hepatotoxicity management (Section 6.4.3.1.1).

Grade 1: Subjects with an isolated Grade 1 rash may continue IP at the investigator's discretion. The subject should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Grade 2: Subjects may continue IP for an isolated Grade 2 rash. However, IP (and all other concurrent medication(s) suspected in the investigators causality assessment including TB treatment medications) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT (see Section 6.4.3.1). The subject should be advised to contact the physician immediately if rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Grade 3 or 4: Subjects should permanently discontinue IP (and all other concurrent medication(s) suspected in the investigators causality assessment should be interrupted) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

The rash and any associated symptoms should be reported as AEs (see Section 6.4.3.9) and appropriate toxicity ratings should be used to grade the events (see Section 11.3).

If the etiology of the rash can be definitely diagnosed as being unrelated to IP and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

A rash that the investigator considers related or possibly related to TB treatment should be managed with reference to applicable product labeling, local guidelines and, where the

re-introduction of TB treatment is applicable, the recommendations outlined in Section 11.6.

Subjects receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information. In any subject treated with ABC, the clinical diagnosis of suspected HSR must remain the basis of clinical decision making. Regardless of HLA-B*5701 status, it is important to permanently discontinue ABC and not re-challenge with ABC (i.e., ABC/DTG/3TC, Ziagen, EPZICOM/KIVEXA, or TRIZIVIR™), if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

6.4.3.9. Petechial Rash

Thrombocytopenia induced by RIF and manifested by petechial rash has been described with high-dose intermittent therapy and also after resumption of interrupted treatment. As this event is reversible and potentially serious, RIF should be immediately and permanently withdrawn. This would also require discontinuation from the study, as the subject must be on a RIF-containing TB treatment regimen.

6.4.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

6.4.4.1. Definition of an AE

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an

AE or SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

6.4.4.2. Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life threatening

NOTE: The term "life threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which

may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct) (or ALT ≥3 × ULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

Note: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.4.5. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

Additionally, diagnostic test results that represent a sign of a clinical condition that is already reported as an AE need not be reported as this would be redundant.

6.4.6. TB-Associated Immune Reconstitution Inflammatory Syndrome

The assessment of the frequency of TB-associated IRIS is one of the secondary study objectives (Section 2.2). In order to achieve this goal, investigators need to carefully document and manage signs and symptoms that could be related to TB-associated IRIS. In addition, the clinical team will review the AE terms and HIV conditions in order to identify TB-associated IRIS cases. Information on X-ray findings and repeat sputum

culture and susceptibility testing may be helpful in distinguishing IRIS from worsening TB disease or development of TB resistance.

This section provides guidance on criteria for TB-associated IRIS diagnosis during the study. TB-associated IRIS assessments will be performed according to the Time and Events schedule (Table 3). If any of the major and/or minor criteria described in this section occur, they should be captured and reported as AEs.

Details on toxicity management for TB-associated IRIS cases are described in Section 6.4.3.3.

IRIS is associated with the initiation of highly active ART for subjects co-infected with HIV-1 and TB. IRIS appears to be associated with severe immunosuppression, the speed of immune reconstitution, and TB severity. The diagnosis of this syndrome is actually a diagnosis of exclusion, after ruling out other diagnoses such as non-response to treatment (including failure to TB treatment due to drug resistance), poor adherence to TB treatment, recurrence of TB, toxicity or drug reaction, neoplasia, and opportunistic infections or other causes of fever. In biological terms, the IRIS could be associated with a burst of specific Th1 CD4+ T cells to tuberculin purified protein derivative, detectable by ELISPOT for IFN-γ.

There are 3 components of the existing case definition for paradoxical TB-associated IRIS [Meintjes, 2008]:

h. Preliminary Requirements

Both of the following requirements must be met:

- Diagnosis of TB, meeting WHO criteria for the diagnosis of either positive or negative sputum smear-positive pulmonary TB or extrapulmonary TB before starting the ART
- Initial response to TB treatment: the subject's condition should be stabilized or improved in the presence of appropriate treatment for TB before starting the ART (e.g., remission of night sweats, fever, cough, weight loss). (Note: This does not apply to subjects starting ART within the first 2 weeks of TB treatment, since this is not sufficient time for the occurrence of clinical response)

i. Clinical Criteria

The onset of IRIS signs and symptoms related to TB should occur within the first 3 months of starting, restarting, or changing the ART regimen for treatment failure.

At least 1 major criterion or 2 of the minor criteria listed below must be present:

Major criteria

- New lymph nodes or increase in existing lymph nodes, cold abscesses, or other focal tissue involvement (e.g., tuberculous arthritis)
- New x-ray findings suggestive of TB or worsening of existing images (e.g. chest x-ray, abdominal ultrasonography, computed tomography or magnetic resonance imaging)

- New onset of CNS TB or worsening of existing disease (meningitis or focal neurological deficit caused by tuberculoma)
- New onset or worsening serositis (pleural effusion, ascites, or pericardial effusion)

Minor criteria

- New constitutional symptoms or worsening of existing symptoms, such as fever, night sweats, or weight loss
- New respiratory symptoms or worsening of existing symptoms such as coughing, dyspnea, or rhonchi
- Recent onset or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

6.4.7. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

This information should be recorded in the specific cardiovascular eCRF within 1 week of when the AE/SAE(s) are first reported.

6.4.8. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

6.4.9. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (see Section 11.2) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 6.4.4.2), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.

Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

6.4.10. Suicidality Monitoring

Subjects with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behavior). Therefore, it is appropriate to monitor subjects for suicidality before and during treatment. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior.

Assessment of treatment-emergent suicidality will be monitored during this study using the C-SSRS, if a validated version in the appropriate language is available for the subject. The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Oquendo, 2003]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Day 1 (Baseline) visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. The C-SSRS is to be administered as a patient-completed questionnaire specified in the Time and Events Table (Table 2). Refer to the SPM for further details on questionnaire delivery and follow-ups.

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (nonserious or SAE) eCRF form on any subject that experiences a PSRAE while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to ViiV/GSK within 1 week of the investigator diagnosing a PSRAE.

6.4.11. Pregnancy

6.4.11.1. Pregnancy Testing

Women of childbearing potential must have a negative pregnancy test at Screening and Day 1 to be eligible for administration of IP. Pregnancy testing will also be conducted according to the Time and Events Table (Table 2) and at any time during the study when pregnancy is suspected.

Additionally, a pregnancy test should also be performed prior to IP re-administration, when IP administration is disrupted for more than 7 days.

6.4.11.2. Time Period for Collecting Pregnancy Information

Information on the occurrence of pregnancies in female subjects will be collected over the period starting at Screening and ending at the final Follow-up visit. Only those pregnancies that occur following the first dose of IP will be reported to the medical monitor. Follow-up information will only be collected for pregnancies occurring from Day 1 to the final Follow-up visit.

6.4.11.3. Action to be Taken if Pregnancy Occurs

Any female who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study. Subjects using DTG must immediately discontinue the IP.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as SAEs.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to ViiV/GSK.

ViiV/GSK's central safety department will also forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

6.4.12. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff personnel are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Beginning at Day 1 and continuing until the follow-up contact, AEs will be recorded.

Serious AEs will be collected throughout the entire study. Any SAE assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV/GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to medical monitor within 24 hours, as indicated in Section 6.4.14.

6.4.13. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?”

“Have you had any (other) medical problems since your last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

6.4.14. Prompt Reporting of Serious Adverse Events and Other Events

Serious AEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to the medical monitor as described in Table 7 once the investigator determines that the event meets the protocol definition for that event.

Criteria for liver chemistry stopping and follow-up criteria are in Section 6.4.3.1.

Table 7 Reporting of Serious Adverse Events and Other Events

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow-up reports to be completed within 1 week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow-up reports to be completed within 1 week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Suspected ABC HSR[a]	1 week	ABC HSR eCRF	1 week	Updated ABC HSR eCRF
ALT≥3×ULN **and** bilirubin≥2×ULN (>35% direct) (or ALT≥3×ULN	24 hours[b]	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable[c]	24 hours	Updated "SAE" data collection tool/"Liver Event" documents[c]
ALT≥5×ULN that persists ≥2 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥8×ULN	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3×ULN or ALT ≥3 fold increase from baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]

ABC = abacavir; CV = cardiovascular; eCRF = electronic case report form; HSR = hypersensitivity reaction; SAE = serious adverse event; ULN = upper limit of normal.

a. ABC HSR eCRF required only if event meets one of the definitions in Section 6.4.4.2.
b. PPD must be contacted at onset of liver chemistry elevations to discuss subject safety.
c. Liver event documents (i.e., "Liver Event eCRF" and "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

The investigator will be required to confirm review of the SAE causality by ticking the 'For Investigators ONLY' box at the bottom of the eCRF page within 72 hours of submission of the SAE.

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.4.14.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

ViiV/GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. ViiV/GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from ViiV/GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements. Reporting of SAEs and other events to ViiV/GSK/PPD is addressed in Table 7.

6.4.14.2. Reporting of ABC Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC develops in subjects receiving ABC as part of their NRTI background regimen, and meets the definition of an SAE as described in Section 6.4.4, then, in addition to reporting the case as an SAE, the ABC HSR eCRF should also be completed within 1 week of the onset of the HSR (see Section 6.4.14).

6.4.15. Other Safety Outcomes

Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 4, must be performed by the central laboratory, Quest Diagnostics, or a laboratory contracted by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events schedule (Table 2). Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided in the Quest Diagnostic Laboratory manual. Reference ranges for all safety parameters will be provided to the site by Quest Diagnostics.

Mycobacterium TB laboratory assessments are to be performed locally and the results must be recorded in the subject's eCRF in accordance with Time and Events schedules (Table 2 and Table 3).

All study-required laboratory assessments will be performed by a central laboratory. If required for cardiovascular events, additional specific local laboratory assessments will be recorded in the specific cardiovascular eCRF (see Section 6.4.7).

6.5. Pharmacokinetics

6.5.1. Pharmacokinetic Endpoints

DTG and EFV concentrations will be evaluated at Weeks 8, 24, 36, and 48 using sparse PK sampling.

DTG and EFV drug concentrations will be analyzed using a population PK modeling approach to evaluate the effects of demographic factors (e.g., weight, age, gender, and race), subject characteristics, and on/off RIF treatment on DTG and EFV PK parameters and variability. DTG PK data obtained from this study may be combined with DTG PK data from previous Phase 3 studies for the population PK modeling. Plasma DTG and EFV PK parameters (AUC0-τ, Cmax, and Cτ) estimated by population PK modeling based on sparse PK sampling will be reported and used in the analysis of correlation with antiviral activities at Weeks 24 and 48.

6.5.2. Pharmacokinetic Sample Collection

Blood samples (2 mL each) will be collected from as many subjects as possible for evaluation of DTG and EFV plasma PK levels. Blood samples should be collected into K2EDTA tubes. The PK sampling visits will occur at Weeks 8, 24, 36, and 48 during the Randomized Phase. For the EFV arm, mid-dosing interval samples will be collected at Weeks 8, 24, 36, and 48. For the DTG arm, 1 sample will be collected for each of the following time points relative to IP dose: pre-dose, 1 to 3 hours post-dose, and 4 to 12 hours post-dose at Weeks 8 and 36 as well as 1 sample pre-dose at Weeks 24 and 48 Table 8. If PK sampling is not performed at the planned visit for any reason then the PK sample collection visit will be rescheduled within 4 weeks of the originally scheduled PK visit. The subject will be provided a new diary card at the rescheduled visit for the next PK visit, if applicable.

Table 8 Pharmacokinetic Sample Schedule

Treatment Arm	Week	Sample Times Relative to Dose
DTG PK	8 and 36	1 sample pre-dose[a] 1 sample 1 to 3 h post-dose[b] 1 sample 4 to12 h post-dose[b,c]
	24 and 48	1 sample pre-dose[a]
EFV PK	8, 24, 36, and 48	1 sample mid-dosing interval[d]

DTG = dolutegravir; EFV = efavirenz; h = hour; PK = pharmacokinetic

a. Pre-dose samples to be collected immediately before the morning dose (i.e. within 15 minutes) which will be taken under observation at the clinic. DTG twice-daily pre-dose sample be drawn as close as possible to 12 hours after the previous dose and DTG once-daily pre-dose sample should be drawn as close as possible to 24 hours after the previous dose.
b. Both sample time points must be obtained **from each subject**.
c. It is acceptable to draw the 4 to 12 hour sample any time between 4 and 12 hours post-dose.
d. Mid-dosing interval samples should be collected in the morning at about 12 hours after the evening EFV dose on previous day.

The Week 8 PK visit is to collect PK data during the TB treatment. If the subject is not on TB treatment at Week 8 due to temporary interruption for the management of toxicity, then PK data should instead be collected 14 to 21 days after RIF reintroduction. The Week 36 PK visit is to collect PK data when the subject has completed TB treatment (i.e., the subject is no longer taking RIF). If the treatment course has been extended because of interruptions, collection of Week 36 data should be delayed until TB treatment completion. The Week 24 and 48 PK data will correspond with the primary and secondary efficacy analysis, respectively. Collection of PK data at multiple visits will provide more robust analysis of inter-occasional variability as well as possible evaluation of dosing compliance.

It is important to collect PK samples according to the following specified procedure.

For subjects randomly assigned to the DTG arm

DTG twice daily - While taking **DTG twice daily** following TB treatment completion it is critical that the pre-dose sample should be drawn as close as possible to 12 hours after the previous dose (target window = 10 to 14 hours after the last dose) and before that morning's dose (i.e., within 15 minutes of the next dose). For the 3 days in advance of a PK clinic visit, the subject must be instructed to plan the dosing of DTG at a time that corresponds with the scheduled PK visit time to allow for a pre-dose sample collection as close to 12 hours after the previous dose.

DTG once daily - While taking **DTG once daily** following TB treatment completion it is critical that the pre-dose sample should be drawn as close as possible to 24 hours after the previous dose (target window = 22 to 26 hours after the last dose) and before that morning's dose (i.e., within 15 minutes of the next dose). For the 3 days in advance of a PK clinic visit, the subject must be instructed to plan the dosing of DTG at a time that corresponds with the scheduled PK visit time to allow for a pre-dose sample collection as close to 24 hours after the previous dose.

After the pre-dose sample is taken, the next dose will be taken under observation at the clinic.

To enhance the quality of PK data collection, subjects will be asked to complete a diary card with the date and time of IP administration prior to the scheduled PK clinic visits. The actual dates and times of DTG dosing during the 3 days of prior to PK sampling as well as the observed dose taken at the clinic, if the subject vomited, and the actual date and time of the PK samples must be recorded on the eCRF.

Note: If a subject presents at the clinic for pre-dose PK sample collection having already taken the morning dose or having missed doses within the previous 3 days, it is recommended to reschedule PK sampling at the earliest next clinic visit. It is not recommended to collect PK samples if date and time of dosing for the previous 3 days cannot be reliably confirmed. Such samples will be discarded and will not contribute to any analyses.

Flexibility is allowed in collecting the post-dose sample (anywhere from 1 to 3 hours and 4 to 12 hours post-dose) so that a range of sample times can be obtained. To achieve this, subjects may choose to remain in clinic until at least 1 hour after taking the DTG dose and may choose to return to the clinic 4 to 12 hours after taking the medication.

For subjects randomly assigned to the EFV arm

For subjects on EFV, the mid-dose samples will be collected in the morning, approximately 12 hours after the previous day's dose. The date and time of the EFV mid-dose sample, as well as the date and time the subject had taken the previous 3 doses of EFV, will be collected and recorded on the CRF.

6.5.3. Bioanalysis of DTG and EFV PK Samples

Plasma will be extracted from the blood samples collected and shipped for determination of DTG and EFV plasma concentrations by validated LC/MS/MS assays under the control of GSK PTS DMPK/Scinovo, the details of which will be included in the SPM. Raw data will be archived at the bioanalytical site (detailed in the SPM).

Once the plasma has been analyzed for DTG and EFV, any plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS DMPK protocol.

6.6. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject at Screening for resistance testing at the central laboratory (or a laboratory contracted by the central laboratory) and on study 'plasma for storage samples' according to the Time and Events schedule in Section 6.1 for potential viral genotypic and phenotypic analyses. In addition, whole venous blood samples will be obtained from each subject to provide plasma for storage samples at the time of re-test for suspected protocol-defined virologic failure as specified in the Quest Laboratory manual.

Details concerning the handling, labeling and shipping of these samples will be supplied separately. Viral genotype will be performed at Screening for study eligibility determination through Quest Diagnostics as well as at location(s) to be described in the SPM. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard Phenosense and GenoSure testing methods for protease (PRO), reverse transcriptase (RT), and integrase assays. In addition, where Monogram Biosciences resistance testing is not possible, resistance testing may also be performed at location(s) to be described in the SPM.

6.6.1. Viral Endpoint

A secondary endpoint of this study will be the incidence of treatment-emergent genotypic and phenotypic resistance to DTG, EFV, and other on-study ART in subjects meeting confirmed virologic withdrawal criteria.

6.6.2. HIV-1 Polymerase Viral Genotyping and Phenotyping

Subjects meeting 'confirmed virologic withdrawal criterion' will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from samples collected at the time of meeting 'suspected virologic withdrawal criterion' (additional subsequent samples may be analyzed); these results will be reported to the investigator as soon as available to provide guidance for election of an alternate regimen.

HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the Baseline isolates from all subjects, if possible. When samples cannot be analyzed by Monogram Biosciences, Baseline isolate resistance testing may be performed at location(s) to be described in the SPM.

6.6.3. HIV-1 Exploratory Analysis

Additional analyses for HIV-1 resistance may, for example, be carried on stored plasma samples from Baseline and other relevant time points. These analyses may include but are not limited to additional viral genotyping and/or phenotyping, as well as other virologic evaluations such as linkage and minority species analyses, low level HIV-1 RNA quantitation, and measurement of viral replicative capacity. HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the Baseline and the last on-treatment isolates from subjects who have HIV-1 RNA >400 c/mL regardless of confirmatory HIV-1 RNA.

6.7. Pharmacogenetic Research

Information regarding pharmacogenetic (PGx) research is included in Section 11.1.

The IEC/IRB and, where required, the applicable regulatory agency, must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (see Section 11.1). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and, therefore, PGx assessments will not be conducted.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK-defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug. Electronic CRFs (including queries and audit trails) will be sent at the end of the study in CD format to GSK to be retained. Each investigator will receive a copy of his or her site-specific data in the same format to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to ViiV/GSK according to ViiV/GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

This study is designed to assess the antiviral effect of treatment with a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily) at Week 48, when administered in combination with dual NRTI therapy. No formal statistical hypothesis testing will be performed.

8.1.1. Sample Size Assumptions

Data from recent DTG studies in treatment-naïve subjects have shown consistent response rates of 88% to 90% at Week 48 with a dose of 50 mg once daily (Table 9). Primary analyses in these studies have shown non-inferiority to RAL 400 mg once daily and superiority to both EFV/TDF/FTC once daily and DRV/r once daily. The proportion of subjects with baseline HIV-1 RNA >100,000 c/mL in the Phase III studies ranged from 25% to 32%; there were few subjects with baseline CD4+ cell counts <50 cells/mm^3.

Table 9 Week 48 Results From Recent Treatment-Naïve DTG Studies

Study	Back-ground NRTI	Endpoint	Active Treatment Response[a]	Comparator/ Control Response	Notes
SINGLE Phase III n=833		HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg +ABC/3TC once daily 88% (87%)[a]	EFV/TDF/FTC once daily 81% (80%)[a]	DTG superior (at Wk 48/96) Baseline: 32% >100,000 c/mL HIV-1 RNA
SPRING-2 Phase III n=822	ABC/3TC or TDF/FTC	HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg once daily 88% (87%)[a]	RAL 400 mg BID 85% (86%)[a]	DTG non-inferior (at Wk 48/96) Baseline: 28% >100,000 c/mL HIV-1 RNA
FLAMINGO Phase IIIb n=484	ABC/3TC or TDF/FTC	HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg once daily 90% (88%)[a]	DRV/r 800 mg/100 mg once daily 83% (80%)[a]	DTG superior at Wk 48 (study continuing to Wk 96) Baseline: 25% >100,000 c/mL HIV-1 RNA
SPRING-1 Phase IIb n=205	ABC/3TC or TDF/FTC	HIV-1 RNA <50 c/mL; TLOVR	DTG 50 mg once daily 90%	EFV 600 mg once daily 82%	DTG 10 mg 91% DTG 25 mg 88% Baseline: 21% >100,000 c/mL HIV-1 RNA

ABC/3TC = abacavir/lamivudine; c = copies; CD4 = helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4); DRV/r = darunavir + ritonavir; DTG = dolutegravir; EFV = efavirenz; EFV/TDF/FTC = efavirenz/tenofovir disoproxil fumarate/emtricitabine; FDA = Food and Drug Administration (United States); HIV = human immunodeficiency virus; mL = milliliter; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RNA = ribonucleic acid; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; TLOVR = time to loss of virologic response; Wk = week.

a. Response rate for subjects with baseline CD4+ cell count ≥50 to <500 cells/mm^3, where available.

Response rates <50 c/mL in the REFLATE study at Week 48 were much lower than seen in the DTG studies (Table 10). The study population included higher proportions of subjects with baseline HIV-1 RNA >100,000 c/mL (46%) and with baseline CD4+ cell counts <50 cells/mm^3 (20%); in particular, the EFV treatment arm had more such subjects than either of the RAL treatment arms. These characteristics are typically associated with a lower response rate for achieving virologic suppression.

Table 10 Week 48 Results from the REFLATE Study

Back-ground NRTI	Endpoint	EFV Once Daily (Response Rate)	RAL Twice-Daily (Response Rate)	Notes
TDF/FTC	<50 c/mL; Missing=Failure	600 mg (67%)	400 mg (76%) 800 mg (63%)	n=51 in each arm Baseline: CD4+ cells <50 c/mL: 27%, 24%, and 10%[a] HIV-1 RNA >100,000 c/mL: 51%, 39%, 47%[a]

c = copies; EFV = efavirenz; HIV = human immunodeficiency virus; mL = milliliter; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RNA = ribonucleic acid; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

a. Percentage of subjects at Baseline in EFV 600 mg, RAL 400 mg, and RAL 800 mg treatment groups, respectively

Rates of withdrawal due to non-fatal AEs were comparable between REFLATE and the DTG studies. There was a higher incidence of deaths in REFLATE (approximately 5% overall versus <1% in DTG studies) with many owing to complications with TB co-infection. Even accounting for differences in the study population, the REFLATE response rates are lower than would be expected based on results seen in the DTG studies. The smaller sample sizes in REFLATE are more sensitive to what may be other chance findings.

Given the exposure data, it is anticipated that DTG twice daily co-administered with RIF will have efficacy comparable to DTG once daily, but a study population with higher proportions of subjects with baseline HIV-1 RNA >100,000 c/mL and lower CD4+ cell counts would have slightly lower responses than seen in the prior DTG studies.

Assuming an 85% response rate for DTG at Week 48, a sample size of 66 to 72 subjects in the DTG arm would have >85% power to detect a response rate of greater than 70% (Figure 4). Although the objective of the study is not to test a statistical hypothesis, the sample size has been chosen to provide an adequate number of subjects for assessing the antiretroviral activity of DTG.

8.2. Study Design Considerations

8.2.1. Sample Size Sensitivity

Figure 4 shows the relationship between study power and sample size, assuming an 85% response rate for DTG, to detect a response rate of greater than 70%. A sample size of 69 subjects has >90% power. Smaller samples (e.g., 65 or greater) have at least 86% power, which is relevant when assessing the primary endpoint in alternate analysis populations (i.e., modified ITT-E).

Figure 4 Relationship Between Study Power and Sample Size

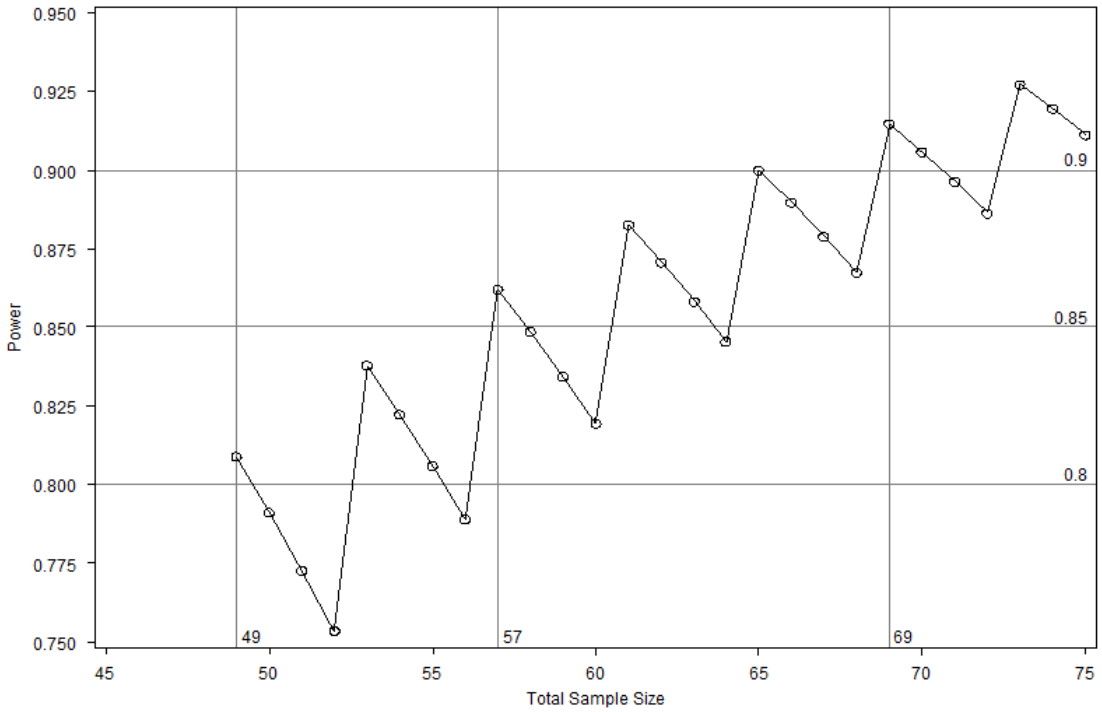
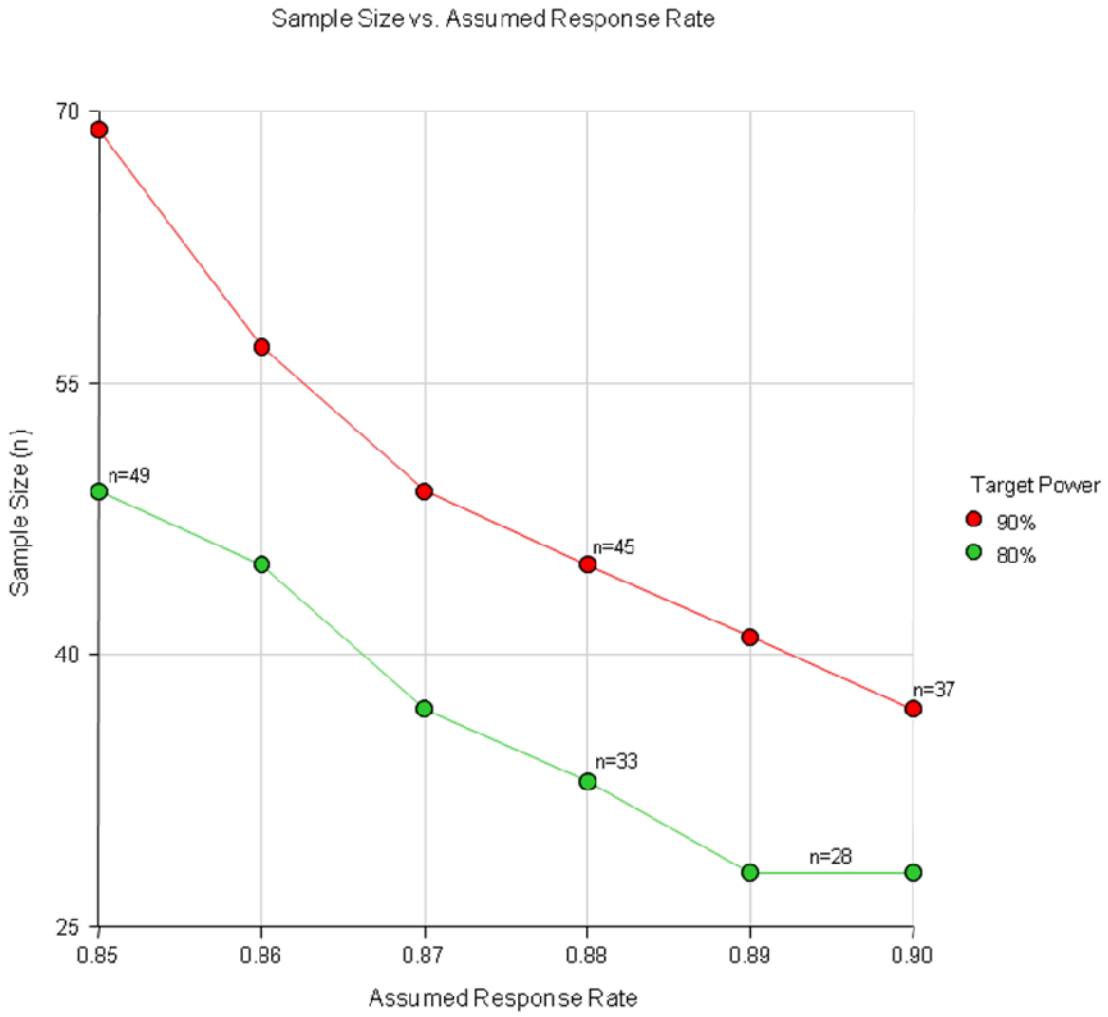


Figure 5 shows the relationship between minimum sample size required and the assumed response rate; different targets for power are considered.

Figure 5 Relationship Between Minimum Sample Size Required and the Assumed Response Rate



8.2.2. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

8.2.3. Analysis Populations

The following populations will be assessed; other analysis populations (e.g., per-protocol, genotypic/phenotypic) will be fully described in the RAP.

8.2.3.1. Intent-to-Treat Exposed (ITT-E) Population

The intent-to-treat exposed (ITT-E) population will consist of all randomly assigned subjects who receive at least one dose of IP. Subjects will be assessed according to their randomized treatment, regardless of the treatment they received. Unless stated otherwise, the ITT-E population will be used for summaries of efficacy.

8.2.3.2. Modified Intent-to-Treat Exposed (MITT-E) Population

The modified intent-to-treat exposed (MITT-E) population will consist of all subjects in ITT-E population with confirmed RIF-sensitive MTB. This population will be used in an additional evaluation of the primary endpoint.

8.2.3.3. Per-Protocol Population

The per-protocol (PP) population will consist of subjects in the ITT-E population with the exception of major protocol violators, e.g. violations which could affect the assessment of antiviral activity. The PP population will be used for sensitivity analyses of the primary efficacy endpoint.

8.2.3.4. Safety Population

The safety population is defined as all subjects who receive at least one dose of IP. Subjects will be analyzed according to the actual treatments received.

8.2.3.5. PK Population

8.2.3.5.1. DTG PK Population

All subjects enrolled in the study who received at least 1 dose and for whom any pre-dose, post-dose, or mid-dose sample was taken for PK analysis with evaluable drug concentration data reported.

8.2.3.5.2. EFV PK Population

All subjects enrolled in the study who received at least 1 dose and for whom any mid-dose sample was taken for PK analysis with evaluable drug concentration data reported.

8.2.4. Analysis Data Sets

Final analysis will be performed after the completion of the study and authorization of final dataset.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by subject, study period or phase, day, and time, noting treatment arm; summaries will be presented by treatment arm, day, and time.

For the primary efficacy analysis, each subject's response (i.e., HIV-1 RNA <50 c/mL) will be calculated according to the US Food and Drug Administration (FDA)'s Snapshot algorithm. This algorithm treats all subjects without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of IP prior to visit window) as non-responders, as well as subjects with ART substitutions not permitted per protocol (see Section 5.1.5).

Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the subject is on-treatment within the visit window of interest (to be specified in the RAP). Full details on this Snapshot algorithm will be contained in the RAP.

For this study, all protocol-permitted substitutions, regardless of HIV-1 RNA results at the time of the substitution, will have no effect on the analysis.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.1 or higher of the SAS system will be used to analyze the data and to generate tables, figures, and listings.

Complete details will be documented in the RAP.

8.2.5. Treatment Comparisons

No formal treatment comparisons will be performed in this study.

8.2.6. Interim Analysis

The first interim analysis will be conducted when all subjects complete their Week 24 visit. The primary analysis will be conducted when all subjects complete their Week 52 visit. A final end-of-study analysis will be conducted when the final subject randomly assigned to the DTG OLE has transitioned to commercial supplies of DTG or has been withdrawn from the study. Further data cuts and analyses may be conducted as necessary in order to support regulatory submissions and publications.

8.2.7. Key Elements of Analysis Plan

When descriptive statistics are used to summarize group characteristics or differences, the following statistics will be included: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

8.2.7.1. Efficacy Analyses

The primary efficacy endpoint, the proportion of subjects from the ITT-E population with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the DTG arm, will be presented with its 95% CI.

The following secondary efficacy endpoints will be summarized using descriptive statistics:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the EFV arm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related AE, safety stopping criteria, or lack of efficacy);
- Changes from baseline in CD4+ counts at Week 24 and Week 48.

The following tertiary efficacy endpoint will be summarized by event type and treatment arm using descriptive statistics:

- Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses, and death);
- Proportion of subjects with TB treatment success (using the WHO definition);
- Proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment.

8.2.7.2. Safety Analyses

Exposure to IP, measured by the number of weeks on IP, will be summarized by treatment arm. The proportion of subjects reporting AEs will be tabulated by treatment arm. The following summaries of AEs will be provided:

- Incidence and severity of all AEs, SAEs, and laboratory abnormalities;
- Proportion of subjects who permanently discontinue IP due to AEs or death;
- Proportion of subjects who temporarily discontinue IP and/or TB therapy due to AEs;
- Proportion of subjects with TB-associated IRIS.

In addition, absolute values and changes over time in laboratory parameters will be analyzed. Laboratory data will be summarized by visit and treatment arm. The number and percentage of subjects with graded laboratory toxicities (based on DAIDS categories, see Section 11.3) will be summarized by treatment arm.

Further details of safety analyses will be included in the RAP.

8.2.7.3. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

Concentrations of DTG and EFV at Weeks 8, 24, 36, and 48 upon initiation of DTG or EFV therapy will be analyzed using population PK modeling approach to estimate AUC, Cmax, and $C\tau$ for individual subjects at Week 48 final analysis. The population PK analysis result will be presented in a separate PK report.

Week 24 interim analyses and Week 48 final analyses of DTG and EFV concentrations based on sparse PK sampling will be summarized using descriptive statistics.

The relationship between DTG/EFV IP exposure and the Week 24 and Week 48 anti-HIV responses (Snapshot) may be evaluated using univariate (and multivariate) logistic regression analysis as well as graphic exploration.

Detailed analysis will be provided in the RAP.

8.2.7.4. Viral Genotyping/Phenotyping Analyses

The incidence of treatment-emergent genotypic and phenotypic resistance to DTG, EFV, and other on-study ART in subjects meeting confirmed virologic withdrawal criteria will be summarized using descriptive statistics.

8.2.7.5. Pharmacogenetic Analyses

See Section 11.1 for details about the pharmacogenetics analysis plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, ViiV/GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH E6(R1) GCP guidelines and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

ViiV/GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described Section 11.1, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and PPD procedures, PPD monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ViiV, GSK, or PPD requirements. When reviewing data collection procedures, the discussion will include identification, agreement, and documentation of data items for which the eCRF will serve as the source document.

PPD will monitor the study to ensure the following:

- Data are authentic, accurate, and complete;
- Safety and rights of subjects are being protected;
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, ViiV/GSK/PPD may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit, or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

Unless terminated early, this study will be considered completed after the last subject transitions to commercial supplies of DTG. Upon completion or termination of the study, the PPD monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and PPD SOPs.

ViiV/GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If ViiV/GSK determines that such action is required, ViiV/GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, ViiV/GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, ViiV/GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. ViiV/GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a ViiV/GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

ViiV, GSK, or PPD will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, ViiV/GSK standard operating procedures, and/or institutional requirements.

The investigator must notify ViiV, GSK, or PPD of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, and Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ViiV/GSK site or other mutually-agreeable location.

ViiV/GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

10. REFERENCES

Babu Swai O, Aluoch JA, Githui WA et al. Controlled clinical trial of a regimen of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. Tubercle. 1988;69(1):5-14.

Bertrand J, Verstuyft C, Chou M et al. CAMELIA (ANRS 1295-CIPRA KH001) Study Group. Dependence of efavirenz- and rifampicin-isoniazid-based antituberculosis treatment drug-drug interaction on CYP2B6 and NAT2 genetic polymorphisms: ANRS 12154 study in Cambodia. J Infect Dis. 2014;209(3):399-408.

Boulle A, Van Cutsem G, Cohen K et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. JAMA. 2008;300(5):530-539

British Thoracic Association (BTA). A controlled trial of six months chemotherapy in pulmonary tuberculosis. Second report: results during the 24 months after the end of chemotherapy. Am Rev Respir Dis. 1982;126(3):460-2.

British Thoracic Society (BTS). A controlled trial of 6 months' chemotherapy in pulmonary tuberculosis. Final report: results during the 36 months after the end of chemotherapy and beyond. Br J Dis Chest. 1984;78(4):330-6.

Cahn P, Pozniak AL, Mingrone H et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382(9893):700-8.

Castagna A, Maggiolo F, Penco G et al. for the VIKING-3 Study Group. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. J Infect Dis. 2014;1-9. [Epup ahead of print]

Centers for Disease Control and Prevention (CDC). Managing drug interactions in the treatment of HIV-related tuberculosis 2013. Available at http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/pdf/tbhiv.pdf. Accessed on 10 April 2014.

Centers for Disease Control and Prevention (CDC). Treatment of Tuberculosis;American Thoracic Society, CDC, and Infectious Diseases Society of America (2003). Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm. Accessed 27 March 2014.

Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax 1998;53(7):536–48.

Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability. The report of final results. Ann Intern Med. 1990; 112(6):397-406.

Department of Health and Human Services (DHHS), Food and Drug Administration and Center for Drug Evaluation and Research. DRAFT Guidance for industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. June 2013. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf. Accessed on 16 October 2013.

Department of Health and Human Services (DHHS), Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed on 28 March 2014 [p.192, K-12 Table 13]

Department of Health and Human Services (DHHS). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-1-infected adults and adolescents: recommendations from the CDC, the NIH, and the HIV Medicine Association of the Infectious Diseases Society of America. June 2013. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed on 27 March 2014 [p.67 and 68; Figure 8 and Figure 9]

Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampicin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013;62(1):21-7.

ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet. 2014; [Epub ahead of print]

Eron JJ, Clotet B, Durant J, et al. for the VIKING Study Group. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis. 2013;207(5):740-8.

European AIDS Clinical Society (EACS) Guidelines for the treatment of HIV infected adults in Europe. Version 7.0. 2013. Available at http://www.eacsociety.org/Guidelines.aspx. Accessed on 09 April 2014

Getahun H, Gunneberg C, Granich R, et al. HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis. 2010;50 Suppl 3:S201-7.

GlaxoSmithKline Document Number 2013N177327_00: ING112574 Clinical Study Report. A Phase III Study to Demonstrate the Antiviral Activity and Safety of Dolutegravirin HIV-1 Infected Adult Subjects with Treatment Failure on an Integrase Inhibitor Containing Regimen (ING112574 –Week48Results of All Subjects Enrolled [N=183]) December 2013.

GlaxoSmithKline Document Number RM2007/00683/07: GSK1349572 Clinical Investigator's Brochure. February 2014.

Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. Lancet Infect Dis. 2014 Apr 9. pii: S1473-3099(14)70711-X. doi: 10.1016/S1473-3099(14)70711-X.

Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011;365(16):1482-91.

Inker LA, Schmid CH, Tighiouart H et al. CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20-9.

International AIDS Society (IAS)-USA. Update of the Drug Resistant Mutations in HIV-1: March 2013. Topics in HIV Medicine 2013;21(1): 6-14.

Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampicin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. Clin Infect Dis. 2013;57(4):586-93.

Meintjes G, Lawn SD, Scano F, et al. International Network for the Study of HIV-associated IRIS. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008;8(8):516-23.

Oquendo MA, Halberstam B, Mann JJ. Risk Factors for suicidal behavior: the utility and limitations of research instruments (2003). In M.B. First [Ed] Standardized Evaluation in Clinical Practice, pp 103-30.

Oxford Textbook of Palliative Medicine, Oxford University Press. Edited by Geoffrey Hanks and Nathan I. Cherny. 1993;109.

Pozniak AL, Coyne KM, Miller RF et al. British HIV Association (BHIVA) guidelines for the treatment of TB/HIV coinfection 2011. HIV Med. 2011;12(9):517-24.

Raffi F, Jaeger H, Quiros-Roldan E et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naïve adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013a;13(11):927-35.

Raffi F, Rachlis A, Stellbrink HJ et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013b;381(9868):735-43.

Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee. Am J Respir Crit Care Med 2006; 174(8): 935–52.

Sirturo (bedaquiline) Product Information, November 2013.

Slutkin G, Schecter GF, Hopewell PC. The results of 9-month isoniazid-rifampin therapy for pulmonary tuberculosis under program conditions in San Francisco. Am Rev Respir Dis. 1988;138(6):1622-4.

Sustiva (efavirenz) EU Product Information, Jan 2014: Viewed on 28 March 2014 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000249/human_med_001068.jsp&mid=WC0b01ac058001d124

Sustiva (efavirenz) US Product Information, May 2013, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020972s043,021360s031lbl.pdf

Tivicay (dolutegravir) EU Summary of Product Characteristics (SmPC). Available at: http://www.viivhealthcare.com/our-medicines/tivicay.aspx. Accessed on 28 March 2014

Tivicay (dolutegravir) US Prescribing Information, August 2013. Available at http://www.viivhealthcare.com/our-medicines/tivicay.aspx. Accessed on 28 March 2014

Török ME and Farrar J. When to start antiretroviral therapy in HIV-associated tuberculosis. N Engl J of Med 2011;365(16):1538-40.

Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369(19):1807-18.

World Health Organization (WHO). Global Tuberculosis Report 2013. Available at: http://www.who.int/tb/publications/global_report/en/. Accessed on 28 Mar 2014

World Health Organization (WHO). Treatment of Tuberculosis: Guidelines – Fourth Edition 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf. Accessed on 28 Mar 2014

11. APPENDICES

11.1. Appendix 1 Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	*HLA-B* 57:01 (Human Leukocyte Antigen B)*	Carriage of the *HLA-B*57:01* variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective *HLA-B*57:01* screening and exclusion of *HLA-B*57:01* positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective *HLA-B*57:01* screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. *HLA-B*57:01* screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.

Drug	Disease	Gene Variant	Outcome
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	*HLA-B*15:02*	Independent studies indicated that patients of East Asian ancestry who carry *HLA-B*15:02* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of *HLA-B*15:02* prior to initiating treatment with carbamazepine.
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	*UGT1A1*28*	Variations in the *UGT1A1* gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular *UGT1A1* gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have 2 copies of the *UGT1A1*28* variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to DTG.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to DTG. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with DTG, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Efficacy
- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety (tolerability and IRIS monitoring)

Study Population

Any subject who is enrolled in the clinical study can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for DNA extraction and used in PGx assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (approximately 6 mL) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of DTG has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to DTG.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (absorption, distribution, metabolism and excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to DTG. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results

of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarise the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

References

Chung WH, Hung SI, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin. Drug Saf. 2010;9:15-21.

Ferrell PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008;9:1543-6.

Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359:1121-2.

Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol. 2004;22:1382-8.

Liu CY, Chen PM, Chiou TJ, et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer. 2008;112:1932-40.

Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002;359:727-32.

Mallal S, Phillips E, Carosi G, et al. PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358:568-79.

Schulz C, Heinemann V, Schalhorn A, et al. UGT1A1 gene polymorphism: Impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. World J. Gastroenterol. 2009;15:5058-66.

11.2. Appendix 2 CDC Classification System for HIV-1 Infections (1993)

Clinical Categories

The clinical categories of HIV infection are defined as follows:

Category A

Category A consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B (Symptomatic non-AIDS conditions)

Category B consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. **Examples** of conditions in clinical Category B include, **but are not limited to**:

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least 2 distinct episodes or more than 1 dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

For classification purposes, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal

candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in clinical Category B.

Category C (AIDS indicator conditions as defined by diagnostic or presumptive measures).

Category C includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

Conditions in Category C include:

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration);or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent

- Toxoplasmosis of brain
- Wasting syndrome due to HIV
- Non-CDC, HIV-associated conditions.

Reference:

- Castro GK, Ward JW, Slutsker L, et al. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992;41(No. RR-17):1-19.

11.3. Appendix 3 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for adverse event (AE) reporting. A grading (severity) scale is provided for each AE term.

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia,	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
and Myalgia				
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult >15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm2 –	Erythema OR Induration OR Edema > 9 cm any diameter (or	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess	Necrosis (involving dermis and deeper tissue)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
		81cm2)	> 81 cm2)	OR Drainage	
	Pediatric ≤15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)		Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL					
Alopecia		Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash		Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation		Slight or localized	Marked or generalized	NA	NA

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children >10 cc/kg) indicated
Hypertension				
Adult >17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Pediatric ≤17 Years (with repeat testing at same	NA	91st – 94th percentile adjusted for age, height, and gender	95th percentile adjusted for age, height, and gender (systolic and/or	Life-threatening consequences (e.g., malignant hypertension) OR

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	visit)		(systolic and/or diastolic)	diastolic)	Hospitalization indicated (other than emergency room visit)
Hypotension		NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion		Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval					
	Adult >16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
	Pediatric ≤16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc					
	Adult >16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
	Pediatric ≤16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diarrhea					
	Adult and Pediatric ≥1 year	Transient or intermittent episodes of unformed stools OR Increase of 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
	Pediatric <1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia		Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis		Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea		Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis		NA	Symptomatic AND Hospitalization not indicated (other than emergency room	Symptomatic AND Hospitalization indicated (other than emergency	Life-threatening consequences (e.g., circulatory failure, hemorrhage,

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
		visit)	room visit)	sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – Pediatric ≤16 Years	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) – Adult ≥18 years See also Seizure: (known pre- existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) – Adult ≥ 18 years For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Seizure – Pediatric <18 years		Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post-ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with <24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without Secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)		NA	Present	NA	NA
Vertigo		Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care Functions
RESPIRATORY					
Bronchospasm (acute)		FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress					
	Adult ≥14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support Indicated
	Pediatric <14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
MUSCULOSKELETAL					
Arthralgia See also Arthritis		Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care Functions
Arthritis See also Arthralgia		Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss					
	Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
	Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
Myalgia (non-injection site)		Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis		NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, Mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
infection)				
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
		control	modification	
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY ***Standard International Units are listed in italics***				
Absolute CD4+ count **– Adult and Pediatric >13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/ mm^3 *200 – 299/µL*	100 – 199/ mm^3 *100 – 199/µL*	< 100/ mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric >13 years** (HIV NEGATIVE ONLY)	600 – 650/ mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/ mm^3 *0.500 x 109 – 0.599 x 10^9/L*	350 – 499/ mm^3 *0.350 x 109 – 0.499 x 10^9/L*	< 350/ mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, >7 days	1,000 – 1,300/ mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/ mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/ mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/ mm^3 *< 0.500 x 10^9/L*
Infant†, 2 – ≤ 7 days	1,250 – 1,500/ mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/ mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/ mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/ mm^3 *< 0.750 x 10^9/L*
Infant†, ≤ 1 day	4,000 – 5,000/ mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/ mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/ mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/ mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Adult and Pediatric ≥57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62 – 5.23 mmol/L*	6.50 – 7.4 g/dL *4.03 – 4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult and Pediatric ≥57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *2.14 – 2.78 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Infant†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 – 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant†, ≤21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59 – 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES *Standard International Units are listed in italics*				
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening	pH > 7.5 with life-threatening

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
				consequences	consequences
ALT (SGPT)		1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)		1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low		16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)					
	Adult and Pediatric >14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
	Infant†, ≤14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
	Infant†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)					
	Adult and Pediatric ≥7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
	Infant†, <7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)					
	Adult and Pediatric ≥7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant†, <7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric <18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high					
	Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL > *27.75 mmol/L*
	Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL > *27.75 mmol/L*
Glucose, serum, low					
	Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL < *1.67 mmol/L*
	Infant†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL < *1.67 mmol/L*
Lactate		ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
LDL cholesterol (fasting)					
	Adult ≥18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL ≥ *4.91 mmol/L*	NA
	Pediatric >2 – <18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL ≥ *4.91 mmol/L*	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric >14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric <1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L	125 – 129 mEq/L	121 – 124 mEq/L	≤ 120 mEq/L

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	130 – 135 mmol/L	*125 – 129 mmol/L*	*121 – 124 mmol/L*	*≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS *Standard International Units are listed in italics*				
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random Collection	1 +	2 – 3 +	4 +	NA
		LABORATORY		
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria, 24 hour collection				
Adult and Pediatric ≥10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *>3.500 g/d*
Pediatric > 3 mo -<10 years	201 – 499 mg/m^2/24 h	500 – 799 mg/m^2/24 h	800 – 1,000 mg/m^2/24 h	> 1,000 mg/ m^2/24 h

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	0.201 – 0.499 g/d	*0.500 – 0.799 g/d*	*0.800 – 1.000 g/d*	*> 1.000 g/d*

11.4. Appendix 4 Country-Specific Requirements

No country-specific requirements exist.

11.5. Appendix 5 Liver Safety Drug Restart or Rechallenge Guidelines

GUIDELINES FOR DRUG RESTART OR RECHALLENGE AFTER STOP FOR LIVER CRITERIA

1. **IP rechallenge** may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if favorable benefit: risk and no alternate medicine available. (Figure 6 and Table 11).
2. **IP restart** may be considered for liver safety events with a clear underlying cause (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis, or hypersensitivity [fever, rash or eosinophilia] and drug not associated with HLA genetic marker of liver injury, when liver chemistries have improved to normal or are within 1.5 × baseline and ALT<2 × ULN).
3. Subjects meeting liver chemistry stopping criteria that present rebound of ALT elevation upon stepwise re-exposure to TB treatment regimen (see Section 6.4.3.1 for suggestion on TB treatment re-introduction regimens) will be considered as having the anti-TB treatment as the likely cause of ALT elevation. If the TB treatment component considered to be the likely cause of the ALT elevation is not RIF and an alternative anti-TB treatment containing RIF can be successfully introduced, the authorization for restarting the IP may be discussed between the investigator and the study medical monitor without the need for approval from the VSLC. If there is no evidence of a relationship between one of the antituberculosis anti-TB treatment regimen components (other than RIF) and the ALT elevation, the case will need VSLC approval to restart DTG (this approval can be ad hoc).

Background: Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies**. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered in 1 month of initial injury [Andrade, 2009]. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- Jaundice or bilirubin ≥2 × ULN with initial liver injury
- Prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- Evidence of drug-related preclinical liability (e.g., reactive metabolites; mitochondrial impairment [Hunt, 2010])

Decision Process for Drug Rechallenge Approval or Disapproval

- Principal investigator (PI) requests consideration of drug rechallenge for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternate treatment.

- Medical monitor and Global Clinical Safety and Pharmacovigilance (GCSP) physician to review the subject's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and complete checklist (Table 11).

- The medical monitor and GCSP physician are accountable to review and agree on the following:

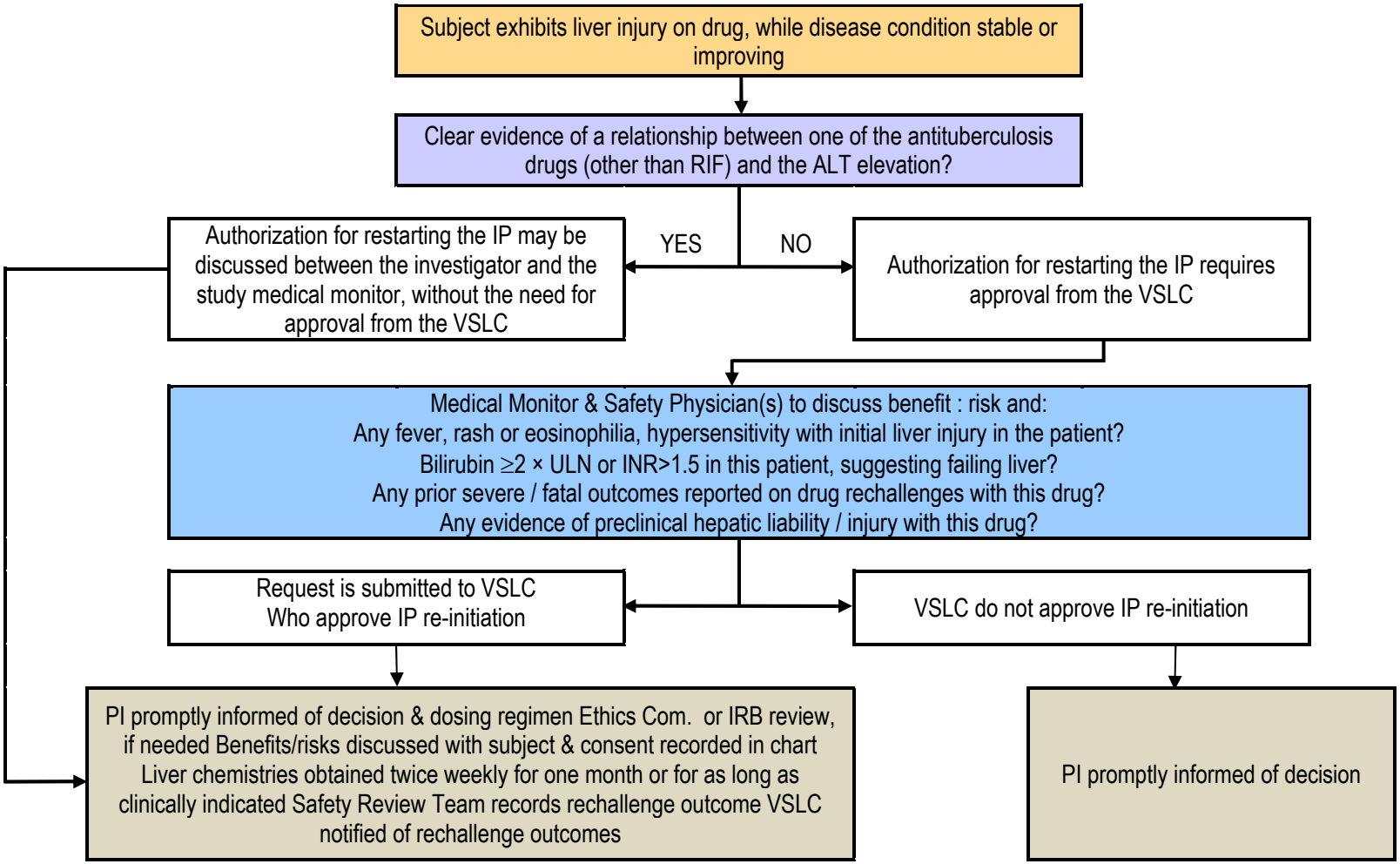
  1. Compelling benefit of the IP for this subject and no alternate therapy
  2. Relative benefit-risk of drug rechallenge, with consideration of the following high risk factors:

     - Initial liver injury event included: fever, rash, eosinophilia, or bilirubin >2 × ULN (or direct bilirubin >35% of total, if available)
     - Subject currently exhibits severe liver injury defined by: ALT >3 × ULN, bilirubin >2 × ULN (direct bilirubin >35% of total, if available), or INR>1.5
     - SAE or fatality has earlier been observed with IP rechallenge
     - IP associated with known preclinical hepatic liability/injury

- Relevant physicians must review and agree on request for drug rechallenge:

  - Safety Team Leader, study medical monitor and Physician Product Leader Medicines Development Leader, and Project Physician Leader (GSK).
  - Medicines Development Leader and Project Physician Leader (GSK).
  - Request is taken to full VSLC for final decision

Figure 6 VSLC Process for Drug Rechallenge Approval or Disapproval



The local operating company (LOC) medical director (ViiV and GSK where applicable) should be informed that IP rechallenge is under consideration and of the final decision, whether or not to proceed.

Table 11 Checklist for IP Rechallenge for Critical Medicine (Following Drug-Induced Liver Injury, IP Rechallenge is Associated with 13% Mortality Across all Drugs in Prospective Studies)

	Yes	No
Relative benefit-risk favorable for drug rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
○ fever, rash, eosinophilia, or hypersensitivity		
○ or bilirubin ≥ 2 × ULN (direct bilirubin >35% of total)		
○ Subject currently exhibits ALT ≥ 3xULN, bilirubin ≥ 2 × ULN (direct bilirubin >35% of total, if available), or INR ≥ 1.5		
○ SAE or fatality has earlier been observed with IP rechallenge **If yes, please provide brief explanation**:		
○ IP associated with known preclinical hepatic liability/injury		
○ Source data defining the subjects current resistance profile		
○ Previous drug history		

Medical monitor, GCSP Physician, and PI actions for Restart or Rechallenge following VSLC decision

Medical Monitor and (Global Clinical Safety and Pharmacovigilance) GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's rechallenge (or restart) decision and recommended dosing regimen in writing and medical monitor must record note in study files.
- The Safety Review Team must record rechallenge (or restart) outcomes and the GCSP Physician must send these to the VSLC
- All severe reactions (rechallenge associated with bilirubin >2 × ULN or jaundice, or INR ≥1.5), SAEs, or fatalities with drug rechallenge (or restart) must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy, and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions

- The PI must obtain IRB or IEC approval of IP rechallenge or restart, as required.
- If IP re-initiation is approved, the subject must provide informed consent with a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.

Targeted IP rechallenge or IP restart informed consent form must be used.

- The subject's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by medical monitor.

- Liver chemistries must be followed ***twice weekly for 'rechallenge'*** cases and ***once weekly for 'restart' cases*** for one month or for as long as clinically indicated following drug re-initiation. If the subject exhibits protocol-defined liver chemistry elevations, IP should be discontinued as protocol specified.

VSLC and the IRB/IEC must be informed of the subject's outcome following drug rechallenge or restart.

Rechallenge/restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting subject stopping criteria
- 2 = recurrent liver chemistry elevation meeting subject stopping criteria
- 3 = serious adverse event
- 4 = fatality

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-14.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatology. 2010;52:2216-22.

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

11.6. Appendix 6 Alternate RIF-Containing TB Treatment Regimens

The WHO-recommended first-line regimen for drug-sensitive TB is a combination regiment of isoniazid and RIF for six months, with ethambutol and pyrazinamide for the first two months. This regimen may be given daily or intermittently according to local or national guidelines. In case alternate TB treatments need to be considered due to tolerability/toxicity issues to one of the agents on the WHO-recommended first line regimen or due to antibiotic resistance, alternative TB treatment regimens are suggested below. The doses used should follow local or national guidelines. For additional information on alternate RIF-containing TB treatment regimens see Section 6.4.3.1.1. None of the alternate RIF-containing TB treatment regimens listed below should be used as the first-line TB treatment.

- **Regimen 1 (omitting pyrazinamide):** isoniazid, RIF, and ethambutol for 2 months, followed by RIF and isoniazid, for 7 months (9 months in total) [BTA, 1982; BTS, 1984; Slutkin, 1988].
- **Regimen 2 (omitting isoniazid):** RIF, pyrazinamide, ethambutol, and streptomycin for 2 months, followed by RIF and ethambutol for 7 months (9 months in total) [Babu, 1988].

  The investigator may find Regimen 2 suitable in cases where isoniazid is found to have precipitated hepatotoxicity (i.e., in the course of TB drug re-introduction for Regimen 1) [BTS, 1984]. In which case, the investigator may choose to use the schedule suggested in Table 6. Guidance from a local expert should be sought.

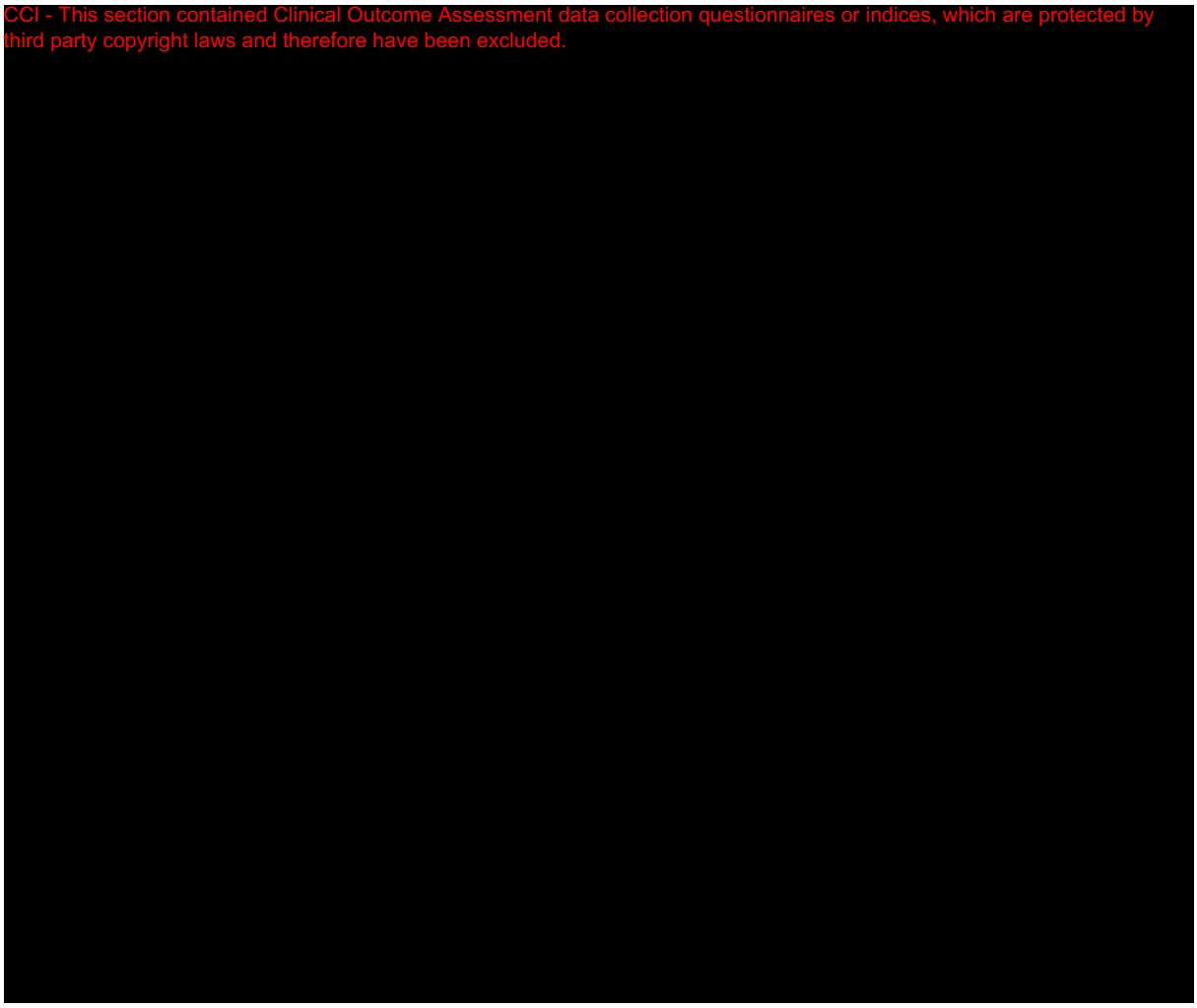
  This is also a suitable regimen for use when the study subject is found to be infected with isoniazid-resistant TB. If the WHO first-line regimen was well-tolerated prior to the discovery of isoniazid-resistance, then it is reasonable for all drugs in Regimen 2 to be introduced simultaneously instead of using the schedule displayed Table 6.
- **Regimen 3 (omitting ethambutol)**: RIF, isoniazid, and pyrazinamide for 2 months, followed by RIF and isoniazid for 4 months [Combs, 1990].

  The investigator may choose to use Regimen 3 for those subjects who are intolerant to ethambutol (the principal adverse effect of ethambutol being optic neuritis). Provided other components of Regimen 3 have been well-tolerated, conversion from the WHO first-line regimen only requires that ethambutol be stopped. Otherwise, the schedule in Table 5 is suitable if there has been a drug-interruption and the investigator feels that a gradual reintroduction is required. Consultation from a local expert should be sought.

When making changes to TB treatment, national or local guidelines on the treatment of tuberculosis should always be followed and take precedence over the recommendations made in this section. Should the subject need to go on a regimen that excludes the use of RIF (e.g., for reasons of tolerability/toxicity or antibiotic resistance), then the subject will have to be withdrawn from the study. Further details describing withdrawal criteria are described in Section 4.5.

11.7. Appendix 7 Karnofsky Performance Status Scale

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



11.8. Appendix 8 Child-Pugh Classification

A subject is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 13). For subjects requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 13 Child-Pugh System

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy Grade 1[a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, SI units (µmol/L), Serum bilirubin, conventional units (mg/dL)	<34 <2	34 to 52 2 to 3	>52 >3
Serum albumin, SI units (g/L) Serum albumin, conventional units (mg/dL)	>35 >3.5	28 to 35 2.8 to 3.5	<28 <2.8
Prothrombin Time (seconds prolonged) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

a. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

References

Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg. 1997 Nov;3(6):628-637

Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:649-649.

11.9. Appendix 9 Protocol Changes

Amendment 01: A global protocol amendment applicable to all participating countries:

Summary of Changes in Protocol Amendment 01 and Rationale

- Mailing address of study medical monitor was updated.
- Changes were made to the protocol text in the following sections to reflect the revision of the number of subjects to be randomized from ~125 to ~115 to alleviate enrolment difficulties and recruit the study in a timely manner. The reduced sample size will allow timely availability of the data while maintaining a high power for the sample size assumption. The changes were made in Protocol Summary Study Design Section, in Section 3.1, in Section 4.1, in Section 8.1.1 and in Section 8.2.1.
- Minor clarifications in the study conduct include clarification of the use of solid media for the 2 month TB culture to be preferred rather than mandated to be aligned with the original study intent to follow national recommendations for TB testing and management. Change was made in Section 3.1.1.
- Correction of the list of participating countries in Sections 3.2 and Section 4.1.
- Minor clarifications on GeneXpert testing or equivalent validated test and the ability to perform the test at the Screening visit in alignment with the original the study design and intent and described in Section 3.1. Changes were made in Sections 4.2 and Section 6.1.
- Addition of instructions for investigators on the new GSK/ViiV procedure requiring investigator to confirm and document their review of the SAE causality within 72 hours of submission of the SAE. Change was made in Section 6.4.14.
- Minor clarification and/or corrections of typographical errors were made in inclusion criteria 19 and 23 Section 4.3, in Section 6.4.14.2 and in Section 8.1 Table 9.
- Figure 6 in Appendix 5 was replaced by an identical and reformatted figure to improve readability.

List of Changes (Old deleted text shown as strike through and new text shown in bold)

- Page 3, SPONSOR INFORMATION PAGE last paragraph:

PPD MD, PhD
PPD
~~1800 Perimeter Park Drive, Suite 275~~**3900 Paramount Parkway, South Building, 3rd Floor, Office 352**

- Protocol Summary Study Design and Section 3.1 first and second paragraph:

This is a Phase IIIb, randomized, open-label study describing the efficacy and safety of DTG and EFV-containing ART regimens in HIV/TB co-infected patients. The study will

be conducted in approximately **(+/-5%)** 1**1**~~2~~5 HIV-1 infected individuals who are ART-naïve with a CD4+ cell count ≥50 cells/mm^3 and newly diagnosed with confirmed pulmonary, pleural, or LN *Mycobacterium* TB (MTB) taking RIF-containing first-line TB treatment. Subjects should have confirmed RIF-sensitive MTB infection as determined by GeneXpert (or equivalent approved molecular test) or mycobacterial culture. Eligible subjects will be randomly assigned in a 3:2 ratio to receive DTG plus 2 NRTIs (approximately **69**~~75~~ subjects) or EFV plus 2 NRTIs (approximately **46**~~50~~ subjects).

- Section 3.1.2, 2nd Paragraph, 2nd sentence:

Sputum will be collected from subjects with pulmonary tuberculosis 2 months after initiating TB treatment (solid media culture testing is **preferred** ~~required~~).

- Section 3.2 Discussion of Design, 2nd paragraph, 1st sentence:

Adult subjects diagnosed (smear positive) and proven RIF-sensitive TB who are initiating TB treatment with HRZE will be recruited at sites in Brazil, Mexico, Russia, **Argentina, Peru,** South Africa~~, Malawi~~ and Thailand.

- Section 4.1, 1st and 2nd paragraph and Table:

A sufficient number of subjects will be screened in order to ensure that a total of approximately **(+/-5%)** 1**1**~~2~~5 subjects will be randomly assigned in a 3:2 ratio to DTG (approximately **69**~~75~~ subjects) and EFV (approximately **46**~~50~~ subjects), respectively.

Assuming 55% of subjects do not meet eligibility criteria, this will require the screening of approximately 2**5**~~7~~5 subjects. Subjects will be enrolled from Brazil, Mexico, Russia, **Argentina, Peru,** South Africa~~, Malawi,~~ and Thailand.

	Subjects
Screened	~25~~7~~5
Randomized	~11~~2~~5
Evaluable	~11~~2~~5

- Section 4.2, Inclusion criteria 7 and 8:

3. New diagnosis of pulmonary, pleural, or LN tuberculosis based on identification of *Mycobacterium tuberculosis* using culture methods or GeneXpert **(or other approved molecular test)** on sputum or on samples collected by needle aspirate of pleural fluid or an affected LN;
4. RIF sensitivity of *Mycobacterium tuberculosis* either by culture or Gene Xpert (or other ~~validated~~ **approved** nucleic acid amplification test);

- Section 4.3, Exclusion criteria 19 and 23:

19. Any verified Grade 4 laboratory abnormality **with the exception of Grade 4 triglycerides. A single repeat test is allowed during the Screening period to verify a result**;

23. Platelet count <50**,**000/mm^3.

- Section 6.1, Table 2, row 8, column 1:

Perform GeneXpert or equivalent and/or Document GeneXpert or **equivalent** RIF-sensitive MTB.

- Section 6.4.14, new sentence added after Table 7:

The investigator will be required to confirm review of the SAE causality by ticking the 'For Investigators ONLY' box at the bottom of the eCRF page within 72 hours of submission of the SAE.

- Section 6.4.14.2, typo corrected:

If a clinically suspected case of HSR to ABC develops in subjects receiving ABC as part of their NRTI background regimen, and meets the definition of an ~~AE/~~SAE as described in Section 6.4.4, then, in addition to reporting the case as an SAE, the ABC HSR eCRF should also be completed within 1 week of the onset of the HSR (see Section 6.4.14).

- Section 8.1.1, Table 9, 3rd column, rows 2 to 5, typo corrected:

~~CD4+ cell count~~**HIV-1 RNA** <50 c/mL

- Section 8.1.1, 5th and last paragraph:

Assuming an 85% response rate for DTG at Week 48, a sample size of ~~75~~ **66 to 72** subjects in the DTG arm would have >~~90~~**85**% power to detect a response rate of greater than 70% **(Figure 4)**. Although the objective of the study is not to test a statistical hypothesis, the sample size has been chosen to provide an adequate number of subjects for assessing the antiretroviral activity of DTG.

- Section 8.2.1, 1st paragraph, 2nd sentence:

A sample size of **69**~~75~~ subjects has >90% power. Smaller samples (e.g., 6**5**~~9~~ or greater) have at least 8**6**~~8~~% power, which is relevant when assessing the primary endpoint in alternate analysis populations (i.e., modified ITT-E).

- Figure 6 in Appendix 5:

Figure 6 was reformatted.